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The Clinical Physiology of Water Metabolism

Part III: The Water Depletion (Hyperosmolar) and Water Excess (Hyposmolar) Syndromes

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Hyperosmolality occurs when there are defects in the two major homeostatic mechanisms required for water balance—thirst and arginine vasopressin (AVP) release. In this situation hypotonic fluids are lost in substantial quantities causing depletion of both intracellular and extracellular fluid compartments. Patients with essential hypernatremia have defective osmotically stimulated AVP release and thirst but may have intact mechanisms for AVP release following hypovolemia. Hyperosmolality can also be seen in circumstances in which impermeable solutes are present in excessive quantities in extracellular fluid. Under these conditions there is cellular dehydration and the serum sodium may actually be reduced by water drawn out of cells along an osmotic gradient.

Hyposmolality and hyponatremia may be seen in a variety of clinical conditions. Salt depletion, states in which edema occurs and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) may all produce severe dilution of body fluids resulting in serious neurologic disturbances. The differential diagnosis of these states is greatly facilitated by careful clinical assessment of extracellular fluid volume and by determination of urine sodium concentration. Treatment of the hyposmolar syndromes is contingent on the pathophysiology of the underlying disorder; hyponatremia due to salt depletion is treated with infusions of isotonic saline whereas mild hyponatremia in cirrhosis and ascites is best treated with water restriction. Severe symptomatic hyponatremia due to SIADH is treated with hypertonic saline therapy, sometimes in association with intravenous administration of furosemide. Less severe, chronic cases may be treated with dichlormethyltetracycline which blocks the action of AVP on the collecting duct.

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ABBREVIATIONS USED IN TEXT

ADH = antidiuretic hormone
AVP = arginine vasopressin
CNS = central nervous system
DI = diabetes insipidus
ECF = extracellular fluid
GFR = glomerular filtration rate
ICF = intracellular fluid
SIADH = inappropriate secretion of antidiuretic hormone

Hyperosmolar Syndromes

The circumstances in which the effective osmolality of body fluids is most likely to be increased above normal are a loss of water from the body in excess of sodium chloride (a hypotonic solution), the addition of a solute that does not freely penetrate cells, such as hypertonic glucose or mannitol, or a combination of both. (For details of these situations, see Table 12 in Part II.) In almost all instances in which there is a net hypotonic loss of water, hypernatremia occurs. Diabetes mellitus and prolonged administration of hypertonic mannitol solution are the only common clinical situations in which profound hypertonic dehydration may occur in the presence of normal or low serum sodium. In patients with uncontrolled diabetes accompanied by progressive hyperglycemia (and in patients receiving hypertonic mannitol), osmotic withdrawal of water from all body cells will cause severe cellular dehydration and dilution of the residual sodium in extracellular fluid (ECF). The extent of the lowering of plasma sodium by hyperglycemia per se can be estimated by multiplying 1.6 mEq per liter times each 100 mg per dl that the plasma glucose is elevated above normal. At times, however, especially in the syndrome of nonketotic hyperglycemic diabetic coma,[237] the magnitude of the water depletion may be so great that despite the profound hyperglycemia (greater than 1,000 mg per dl), which is so characteristic of this syndrome, the serum sodium will be normal or, more frequently, significantly elevated (greater than 145 mEq per liter).

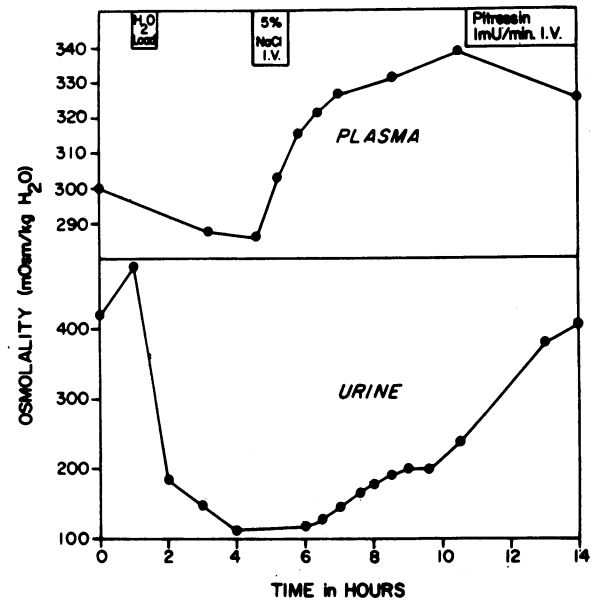
Investigators have become increasingly aware of the hypernatremic-hyperosmolar syndrome associated with hypertonic (glucose) peritoneal dialysis.[238] The latter (4.5 percent glucose added to the isotonic dialysis fluid) is commonly used to treat intractable edematous states, especially in association with severe renal failure. When this hypertonic solution is put into the peritoneal cavity, water moves along its osmotic gradient into the peritoneal cavity and extracellular electrolytes follow by diffusion. However, the glucose (4,500 mg per dl in the dialysis fluid) diffuses rapidly into the bloodstream, elevating blood glucose to values of 500 to 1,000 mg per dl. The pronounced extracellular hyperglycemia and hyperosmolality rapidly draw water out of all cells and dilute the salts of the ECF. The concentration of sodium in the blood and the ECF during this continuing unsteady state will fall below the sodium concentration in the dialysis fluid, thereby establishing a gradient for sodium and chloride to diffuse from the peritoneal cavity into the ECF. The net effect of this process at the end of the peritoneal dialysis is the removal of water in excess of isotonic proportions of sodium. When the hypertonic glucose in the ECF is metabolized by the patient, usually over 12 to 14 hours, the blood sugar returns to normal, the osmotic effect of the hyperglycemia disappears, water moves back into the dehydrated cells and the sodium and chloride concentrations in the blood and the ECF rise to hypernatremic levels. It is apparent that this hypernatremia will prevent the complete rehydration of all body cells. This whole syndrome can be prevented or minimized by using the least hypertonic dialysis fluid necessary to achieve the desired negative fluid balance, such as 1.5 percent alternating with 3 percent to 4 percent glucose, and by giving the patient adequate free water orally or parenterally to take care of all insensible and renal losses occurring during the dialysis.

Hypertonic dehydration is particularly prone to occur in elderly or unconscious patients who cannot respond to the thirst stimulus or who cannot adequately request water when it is needed. Furthermore, these persons are often tube fed a high-protein mixture or given parenteral hyperalimentation. Very often a large part of the administered protein or amino acids is not retained but is converted to urea, and the excretion of the latter causes a sustained osmotic diuresis. This, like any other osmotic diuresis, will produce large urinary volumes that are hypotonic with respect to sodium. The relatively high rate of urine flow falsely assures the physician that the patient is getting an adequate intake of fluid. In reality, a progressive contraction of body water is taking place. Peters referred to the pathophysiologic events accompanying profound water loss as the "rehydration reaction." This consists of a low urinary water

volume, a high urinary concentration and excretion of potassium, and, in spite of hypernatremia, a low concentration and excretion of urinary sodium.

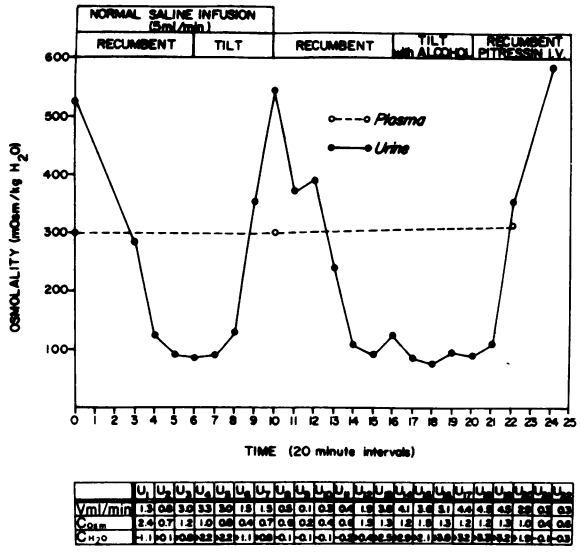
The unusual condition found in a group of patients of hypernatremia and hyperosmolality accompanied by supposedly normal hydration, and its differentiation from other sustained hyperosmolar states (see Table 12 in Part II), has been reviewed in detail by DeRubertis and associates.[38] They carefully investigated this syndrome in a patient in whom the condition had resulted from histiocytosis involvement of the hypothalamus. Abnormalities in water metabolism associated with lesions in this area appear to result from (1) impaired thirst, (2) impaired arginine vasopressin (AVP) production and secretion (diabetes insipidus) and (3) altered regulation of vasopressin secretion. These disturbances may occur either singly or in combination. DeRubertis has outlined the physiologic characteristics of those patients with hypernatremia and possibly normal hydration as follows. The sustained hypernatremia is usually not associated with a significant deficit of ECF volume as reflected by an absence of oliguria, azotemia or decreased urinary sodium content. The spontaneous fluid intake is generally low relative to the elevated plasma osmotic pressure, indicating defective thirst. In addition, the release of antidiuretic hormone (ADH) in response to osmotic stimuli appears impaired. However, endogenous ADH production is at least partially intact as implied by the concentration of urine under certain circumstances. In several of these patients hyperosmolality was not completely corrected by acute or chronic fluid loading, excluding inadequate fluid intake as the predominant factor in the disruption of osmotic homeostasis. It has been suggested that the sustained hyperosmolality in this group was the result of an elevated osmotic threshold for release of ADH. With such a disturbance in the osmotic regulation of ADH secretion, urine would be concentrated and water conserved only at very high levels of plasma osmolality. Thus, a new steady state at a high plasma osmolality would be maintained by this proposed upward "resetting of the hypothalamic osmostat."

This hypothesis for the cause of the hypernatremia appears to be supported in the patient studied by DeRubertis and associates. During 23 days of observation, in which the patient was receiving a normal diet and ad libitum water intake, plasma sodium fluctuated between 148 and 160 mEq per liter and plasma osmolality between 298 and 323 mOsm per liter. Endogenous AVP release was indicated by urine osmolalities as high as 710 mOsm per liter during water restriction, but only after a rise in plasma osmolality to 326 mOsm and a weight loss of 1.4 kg. Fluid intakes as high as 6 liters per day did not lower plasma osmolality, but merely led to a prompt water diuresis, indicating that simple water deficiency was not the cause of the hypernatremia. Hypertonic saline infusion during water diuresis, while causing a prounced increase in plasma osmolality, resulted



	U_1	U_2	U_3	U_4	U_5	U_6	U_7	U_8	U_9	U_{10}	U_{11}	U_{12}	U_{13}	U_{14}	U_{15}	U_{16}
V ml/min	1.0	0.8	2.9	2.5	2.4	2.7	16.5	18.3	11.9	4.5	11.5	8.2	5.1	8.3	5.4	6.3
C_{Osm}	1.4	1.3	1.8	1.3	1.0	1.0	6.4	8.3	6.0	2.4	6.7	5.0	3.1	5.9	3.6	7.6
C_{H_2O}	-0.4	-0.5	+1.1	+1.2	+1.4	+1.7	+10.1	+10.0	+5.9	+2.1	+4.8	+3.2	+2.1	+2.4	-0.4	+1.3

Figure 36.—Response to hypertonic saline infusion. After establishment of a water diuresis with an oral water load (H_2O load), 20 ml per kg of body weight, infusion of hypertonic saline (5 percent NaCl) given intravenously at 0.1 ml per kg of body weight per minute did not result in urinary concentration despite a pronounced acute rise in plasma osmolality (52 mOsm per kg of water, 18 percent in six hours). Rather, urinary (U) flow (maximum 18.3 ml per minute) increased with saline infusion. The maximum values were noted 90 minutes after cessation of the infusion. Water diuresis, still in progress at hour 10, was terminated with exogenous vasopressin (Pitressin, 1 mU per minute, given intravenously). Table, at bottom, depicts volume (V), osmolar clearance (C_{Osm}) and free water clearance (C_{H_2O}) in milliliters per minute, for individual determinations corresponding in sequence to points plotted for urine osmolality. (Reproduced with permission from DeRubertis FR, Michelis MF, Beck N, et al: J Clin Invest 50:97-111, 1971.)



	U_1V_1	U_2V_2	U_3V_3	U_4V_4	U_5V_5	U_6V_6	U_7V_7	U_8V_8	U_9V_9	$U_{10}V_{10}$	$U_{11}V_{11}$	$U_{12}V_{12}$	$U_{13}V_{13}$	$U_{14}V_{14}$	$U_{15}V_{15}$	$U_{16}V_{16}$	$U_{17}V_{17}$	$U_{18}V_{18}$	$U_{19}V_{19}$	$U_{20}V_{20}$	$U_{21}V_{21}$	$U_{22}V_{22}$	$U_{23}V_{23}$	$U_{24}V_{24}$	$U_{25}V_{25}$
V ml/min	1.3	0.6	3.0	3.3	2.6	1.5	1.9	0.5	0.1	0.3	0.4	1.6	2.6	4.1	3.6	8.1	4.4	4.5	4.6	2.8	0.5	0.3		
C_{Osm}	2.4	0.7	1.2	1.0	0.8	0.4	0.7	0.6	0.2	0.4	0.5	1.5	1.3	1.2	1.8	1.3	1.2	1.5	1.3	1.6	0.4	0.6		
C_{H_2O}	-1.1	-0.1	-0.6	-2.2	-1.8	-1.1	-1.0	-0.1	-0.1	-0.1	-0.2	-0.4	-0.2	-0.2	-1.1	-6.8	-3.2	-3.2	-3.2	-1.8	-0.1	-0.3		

Figure 37.—Interruption with orthostasis of a water diuresis induced by normal saline infusion. After overnight dehydration, a water diuresis was established during recumbency with normal saline infusion (5 ml per minute). Tilting to 75° for 90 minutes resulted in urinary concentration with urinary osmolality rising from 87 to 543 mOsm per kg of water. Water diuresis resumed with recumbency. Tilting was repeated 15 minutes after oral administration of ethanol-alcohol. Urinary concentration was not observed. During this study urine was collected at 20-minute intervals by an indwelling bladder catheter. Table, at bottom, depicts V, C_{Osm} and C_{H_2O} in milliliters per minute for individual determinations corresponding in sequence to points for urine osmolality. (Abbreviations the same as in Figure 36.) (Reproduced with permission from DeRubertis FR, Michelis MF, Beck N, et al: J Clin Invest 50:97-111, 1971.)

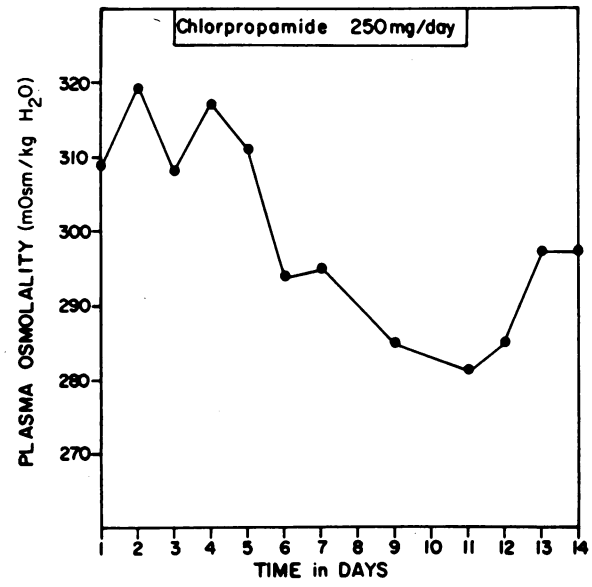


Figure 38.—Response to chlorpropamide. A significant fall in plasma osmolality (P_{Osm}) was noted on the fourth day of therapy with 250 mg of chlorpropamide per day. Response persisted for two days after cessation of the drug. Subsequent readministration of chlorpropamide resulted in a sustained lowering of P_{Osm}. (Reproduced with permission from DeRubertis FR, Michelis MF, Beck N, et al: J Clin Invest 50:97-111, 1971.)

in the excretion of an increased volume of hypotonic urine (Figure 36). An isotonic saline infusion, initiated during hydropenia, resulted in a water diuresis that continued despite a rise in the plasma osmolality from 302 to 320 mOsm per liter. The diuresis was terminated by orthostasis and resumed with return to the recumbent position (Figure 37). Antecedent alcohol ingestion blocked the antidiuresis of orthostasis (Figure 37).

These experimental observations indicate that the neurohypophysis was unresponsive to osmotic stimuli, but responded promptly and normally to nonosmotic volume changes of baroreceptor stimuli. In the steady state, the patient's extracellular volume (inulin space) was slightly below normal (11.2 liters with a predicted normal of 12), as was her blood volume of 3.3 liters with a standard normal of 3.7, corrected to height and lean body weight. DeRubertis suggested that the wide abnormal swings in random plasma osmolality (between 298 and 323 mOsm per liter) indicated that the altered AVP was not simply due to a resetting of the "osmostat," but was the consequence of (1) the loss of the sensitive osmotic regulation of AVP secretion, which normally maintains plasma osmolality at a relatively constant value, and (2) intact volume (baroreceptor) modulation of AVP secretion, which would result in relatively normal overall water balance but a less stable plasma osmolality.

The patient was given chlorpropamide orally in a dosage of 250 mg per day, which resulted in a return of plasma osmolality to a normal level after eight to ten days of therapy (Figure 38). Mahoney and Goodman[223] also successfully used chlorpropamide in a remarkably similar case of a patient with chronic hypernatremia. Bode and co-workers described a restoration of thirst with subsequent enhancement of oral water intake and amelioration of hypernatremia in patients with hypodipsia and diabetes insipidus (DI).[228] This effect on thirst suggests a possible central nervous system (CNS) site for action of chlorpropamide.

Chlorpropamide may be completely effective in this syndrome for two reasons, both based on its ability to substantially augment the presence of small amounts of AVP in the circulation. (1) A rise above normal in plasma osmotic pressure in

these patients may still have caused a minimal release of AVP into the circulation which, in the presence of the chlorpropamide, effectively increased water transport in the distal nephron, but in the drug's absence was ineffective. (2) Or, despite the complete absence of osmotic release of AVP in these patients, chlorpropamide so enhanced the action of minimal amounts of AVP in the circulation that the smallest volume deviations from normal were *adequate* to supply the minimal amount of hormone needed, given the presence of chlorpropamide, but *not adequate* in the drug's absence. These effects would complement any enhancement of thirst that might occur. The continued lethargy and clouded sensorium observed in these patients cleared completely when plasma sodium and osmolality returned to normal with therapy. DeRubertis and co-workers have subsequently described additional cases of essential hypernatremia.[239] In these cases and in others from the literature, there was evidence of *normovolemia,* intact nonosmolar secretion of AVP and defective osmolar stimulation of AVP. The absence of thirst seemed to play an important role in the pathogenesis of the hypernatremia. However, this could not be the entire explanation because oral water loading failed to correct the disorder. They pointed out that exogenous vasopressin returned levels of plasma sodium to normal, which suggested that AVP deficiency had a considerable role in the perpetuation of the hypernatremia.

It is not clear, however, whether such patients are truly normovolemic. Hypernatremia must be due to either a renal water loss in excess of water intake with normal total body sodium or to sodium excess. There is no evidence for the latter. Under conditions of water deficiency one would assume that both cellular and extracellular dehydration would be present and body fluid volumes reduced.

In recent years there have been several well-documented reports of hypernatremia in patients with severe plasma volume contraction.[240,241] These cases may represent a more extensive involvement of the hypothalamic-posterior pituitary system with simultaneous impairment of both osmolar and volume stimulation of thirst and AVP secretion. Urine volumes are kept normal because of renal and extrarenal factors that contribute to water retention in this condition. The low level of residual circulating AVP, when combined with (1) a decreased glomerular filtration rate (GFR)

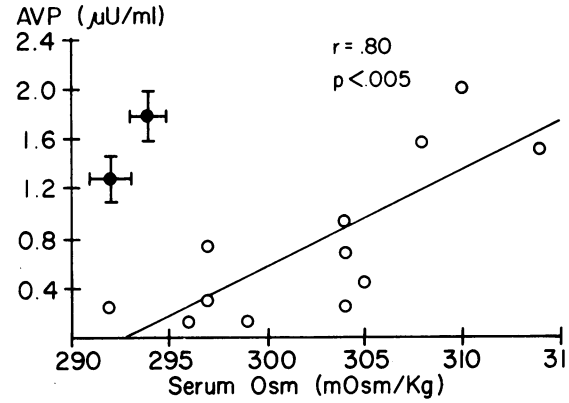


Figure 39.—Plasma arginine vasopressin (AVP) values plotted as a function of plasma osmolality in a patient with adipsia and hypernatremia (open circles). The mean values for plasma AVP and osmolality for 24 normal subjects after 12 and 18 hours of water deprivation (solid circles) are shown for comparison. Plasma AVP rose progressively with increasing plasma osmolality in this patient but always remains inappropriately low relative to plasma tonicity. Plasma AVP did eventually approach the normal range, but only at the expense of substantial hyperosmolality. (Replotted with permission from data of Grubb SR, et al: J Clin Res 25: 13A, 1977, and Weitzman R: unpublished data.)

and renal blood flow, (2) enhanced reabsorption of solutes and water proximal to the collecting duct, (3) enhanced medullary tonicity over that observed in the nondehydrated state and (4) enhanced vasopressin-independent water reabsorption in the collecting duct as a consequence of the low rate of water flow through this segment, will result in the absence of polyuria as observed in these cases.

Sridhar and colleagues[242] described a case of a 17-year-old girl who had originally had transient polydipsia and polyuria two years earlier and then presented with severe hyponatremia and hypovolemia unresponsive to oral water loading. When the urine to plasma (U/P) osmolar ratio was plotted as a function of serum sodium, it became apparent that the patient was capable of concentrating urine if the serum osmolality were sufficiently elevated. However, these investigators felt that the data did not support the concept of an elevated osmotic threshold for AVP release but, rather, suggested impaired AVP release at all levels of serum osmolality. A similar conclusion can be reached from the findings of Grubb and colleagues in their study of a unique case of a patient with adipsia following an episode of tuberculous meningitis in whom vasopressin-resistant hyposthenuria from streptomycin therapy also developed.[243] Levels of plasma

AVP were determined under varying conditions of hydration and were plotted as a function of plasma osmolality (Figure 39). In some instances, plasma AVP levels were well within normal range but this occurred only under circumstances of extreme hyperosmolality. As in the case described by Sridhar and associates,[242] there was considerable impairment of AVP secretion at all levels of plasma osmolality. In such patients, what little AVP release is observed after dehydration might be stimulated in part by relative hypovolemia.

Halter and co-workers[244] studied a case of chronic hypernatremia and hypodipsia in a patient, and found that although plasma AVP levels were inappropriately low for the given level of plasma osmolality, the patient was capable of substantially elevating plasma AVP after hypovolemic stimulation (Figure 40). As in the case described earlier, there was a significant correlation between plasma AVP and osmolality but with distinctly subnormal values for any degree of osmolality. The hypernatremia in these cases could be due to dysfunction of osmoreceptor stimulation of thirst and AVP release to spare magnocellular neurons for AVP synthesis. One might speculate that subsequent involvement of the supraoptic and paraventricular nuclei could eliminate even hypovolemic-stimulated AVP release which would result in deterioration of volume homeostasis, and profound hypovolemia. Thus, there may be a spectrum of disorders due to qualitative and quantitative defects in the separate components regulating thirst and AVP release (Table 13).

There is evidence for a functional and anatomic separation of the osmoreceptors for thirst from those for AVP release as well as from the neurosecretory neurons (see Figure 3 in Part I). It is possible to envisage a disease process selectively involving the magnocellular neurons in the hypothalamus or the axons traversing the pituitary stalk but sparing the thirst centers in the anterior hypothalamus. In this situation, renal water losses would produce hypertonicity of ECF which would, in turn, result in osmotically stimulated polydipsia and polyuria. The same clinical syndrome could also be produced by a disease process directly involving the osmoreceptors for AVP release but not those for stimulation of thirst. If the disease progressed further to impair the osmoregulation of thirst, polydipsia would cease and urine volumes would be reduced despite the continuing deficiency of AVP secretion. Renal water loss and impaired thirst would result in hypernatremia while nonosmolar stimulation of AVP would tend to minimize volume contraction. Finally, if the nonosmotic regulation of AVP secretion is impaired (probably by involvement of the magnocellular neurons themselves), then severe hypovolemia would ensue.

The proposed mechanism for hypernatremia associated with overhydration syndromes, such

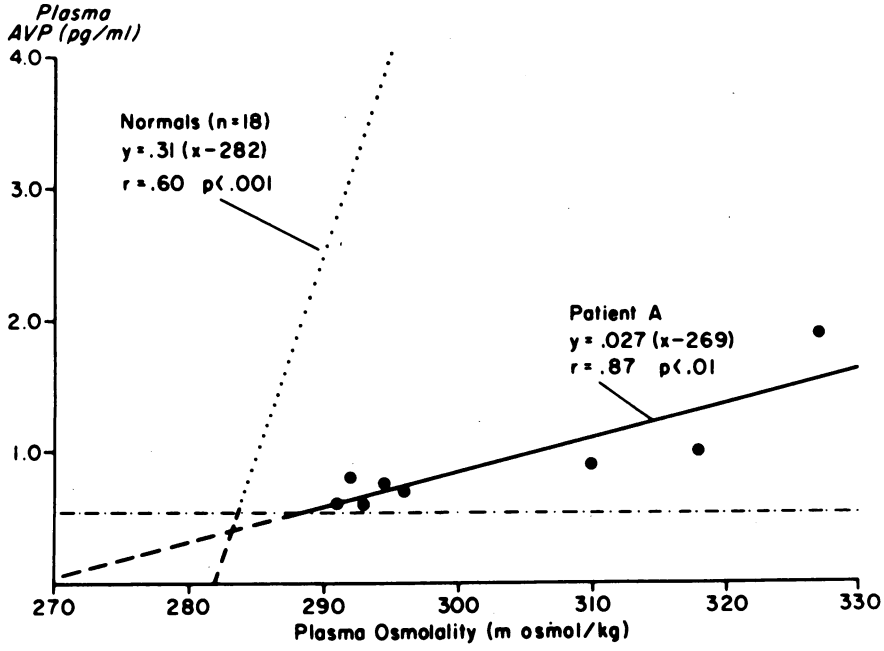


Figure 40.—Regression analysis of plasma arginine vasopressin (AVP) versus plasma osmolality (P_{Osm}) during hypertonic saline infusion in a patient with essential hypernatrema compared with the regression line for the plasma AVP-P_{Osm} relationship during hypertonic saline infusion in 18 normal subjects. The horizontal broken line represents the sensitivity limit of the plasma AVP assay (0.5 pg per ml). (Reproduced with permission from Halter JB, Goldberg AP, Robertson GL, et al: Selective osmoreceptor dysfunction in the syndrome of chronic hypernatremia. J Clin Endocr Metab 44:609, 1977.)

as primary hyperaldosteronism, was described earlier.

Clinical Manifestations of the Hyperosmolar Syndromes

If a patient is conscious, thirst may be extreme, unless there is a hypothalamic lesion causing defective thirst regulation. Severe hyperpnea may be present which does not resemble the deep, rapid breathing of Kussmaul respiration. Invariably there are significant alterations in the sensoria resulting in confusion, stupor and, eventually, coma. Almost any type of focal CNS neurologic syndrome may accompany the altered sensorium. Convulsions may occur rarely, and xanthochromatic or sanguineous spinal fluid may be found, confusing the diagnosis. The latter is due to a substantial increase in permeability or even rupture of the fine capillaries of the brain and subarachnoid space caused by the pronounced contraction of the brain, secondary to its osmotic water loss. Macaulay and Watson have shown that some children with no antecedent neural disorder but who survive from severe hypertonic dehydration, may be left with a state of generalized cerebral dysfunction characterized by impairment of intellect, clumsiness, hyperactivity and difficulty in social adjustment.[245] The most severe CNS dysfunctions are seen at both ends of the age spectrum and the more rapidly the hyperosmolality develops. Arieff and associates[246] have clearly shown that given time, the brain protects itself from dehydration by generating osmotically active substances ("idiogenic osmoles") which minimize the degree of water loss from the brain for any given increase in osmolality of the blood.

The skin and mucous membranes become extremely dry and usually erythematous. In contrast to dehydration associated with salt depletion, the actual skin turgor may remain fairly normal. However, hypotension, tachycardia and, at times, even hyperthermia without a discernible cause may be seen. Oliguria may be present, unless an osmotic diuresis is simultaneously occurring or a polyuric syndrome (see Table 12 in Part II) with hypotonic urine prevents renal water conservation. The concentration of hemoglobin and plasma proteins, as well as the hematocrit, will be elevated.

Water replacement using hypotonic solutions is the basic therapy of hyperosmolar states associated with water depletion. As the loss of water in this form of dehydration is derived proportionately from all fluid spaces, it is possible to calculate the magnitude of the deficit from the observed serum sodium concentration and the assumed normal total body water.[247] For example, an increment of 20 percent in the concentration of sodium (assuming no significant loss of total body solutes) will indicate a reduction of 20 percent in total body water. Therefore, the ratio of normal serum sodium over the observed serum sodium multiplied by the assumed normal body water (60 percent of the usual body weight) will approximate the total volume of free water to be replaced. This can be administered parenterally in the form of 2.5 percent to 5 percent glucose in water or hypotonic (75 mEq per liter) saline, in an amount calculated to return the serum osmolality to normal. Tap water can be taken orally, if possible, and tap-water enemas will be very rapidly absorbed from the rectosigmoid colon. However, it is critical not to correct the hyperosmolar state too rapidly. When rehydration and reexpansion of the brain are excessively rapid, convulsions and coma may ensue. An interval of 48 to 72 hours should be a reasonably safe period in which to return to an euosmolar state. The cause of the hypertonic dehydration should be corrected, if possible, and measures taken to avoid its occurrence. Any undiagnosed comatose,

TABLE 13.—*Development of Hypernatremia Owing to Progressive Disease of the Hypothalamic Centers for the Regulation of Thirst and AVP Release*

	*Polyuric Diabetes Insipidus**	*Normovolemic Hypernatremia*	*Hypovolemic Hypernatremia*
Osmolar regulation of AVP secretion	−	−	−
Thirst	+	−	−
Nonosmolar regulation of AVP secretion, (hypovolemia, hypotension or pressure)	+	+	−
Serum sodium	+↑	+↑	+↑

−=absent; +=present; ↑=increased; AVP=arginine vasopressin.

*This syndrome could also be produced by selective destruction of the neurosecretory neurons or their axons in traversing the pituitary stalk, in which case nonosmolar stimulation of AVP secretion would be absent.

stuporous or confusional state in a child or adult who appears dehydrated should suggest this hypertonic dehydration syndrome.

Hyposmolar Syndromes

As water moves freely across all cell membranes along established concentration (osmolar) gradients, any lowering of ECF osmolality will result in an osmotic disequilibrium which, in turn, will produce a net flux of water from the ECF into the cells until osmotic equilibrium is reestablished. The resulting expansion of intracellular volume may alter cellular function and lead to definite symptoms. This is especially pronounced in the CNS where lethargy, seizures and coma may ensue.

In general, hyposmolality and hyponatremia are either synonymous or reflect each other. However, the presence of a lower than normal serum sodium concentration does not always imply the presence of hyposmolality. In patients having substantial elevations of either serum lipid or serum protein concentration, there is an artifactual reduction in the measured serum sodium concentration (Table 14). This is because the sodium is dissolved only in the water phase of the plasma. This phase normally amounts to 93 percent to 94 percent of a given unit of plasma volume. When there is a very large proportion of lipid or protein per milliliter, the water phase is proportionately reduced. Thus, while the concentration of sodium in *plasma water* appears normal, the concentration per milliliter or per liter of *plasma* is artifactually low. One can calculate the depression in measured serum sodium under these circumstances by multiplying the concentration of lipid in mg per dl by 0.002 or the elevation in serum protein concentration greater than 8 grams per dl by 0.25. In contrast, the osmolality or freezing-point depression of the plasma is not influenced by its fat or protein content. Therefore, osmolality can be correctly measured and the laboratory abnormality confirmed by finding a disproportionate reduction in sodium concentration relative to osmolality in the lipemic or substantially hyperproteinemic plasma.

A pathophysiologic situation in which hyponatremia is not associated with hyposmolality of ECF occurs when there are high concentrations of solutes of low molecular weight localized in the ECF compartment (Table 14). This can occur after intravenous infusion of large amounts of mannitol or glucose, or in patients with diabetes mellitus accompanied by severe hyperglycemia.

TABLE 14.—*Differential Diagnosis of Hyponatremia*

Hyponatremia category	Celluar dehydration	Artifactual	Hypovolemic	Minimal hypovolemic	Hypovolemic
Cause	Hyperglycemia, mannitol infused	Profound hyperlipidemia or hyperproteinemia	Salt depletion, third space	SIADH, myxedema	Cirrhosis, CHF, nephrosis
Status of ECF osmolality	Hyperosmolar hyponatremia	Euosmolar hyponatremia	Hyposmolar hyponatremia	Hyposmolar hyponatremia	Hyposmolar hyponatremia
ECF	↑ or ↓	Normal	↓	Normal or slightly ↑	↑
ICF	↓	Normal	↑	↑	↑
"Effective blood volume"	↑ or ↓	Normal	↓	Slightly ↑	↓
AVP	↑ or ↓*	Normal	↑†	↑†	↑†
PRA	Normal	Normal	↑	↓	↑
U_{Na^+}	Normal	Normal	↑ or ↓‡	↑	↓
Treatment					
Mild (symptomatic)	Treat underlying condition	Treat underlying condtion	Isotonic saline	Water restriction	Water restriction, treat underlying condition
Severe (symptomatic)	Treat underlying condition	Treat underlying condtion	Hypertonic saline	Hypertonic saline with furosemide, mannitol and dichlormethyltetracycline (Declomycin)	Hypertonic saline with furosemide

↑ = increased; ↓ = decreased; AVP = arginine vasopressin; CHF = congestive heart failure; ECF = extracellular fluid; ICF = intracellular fluid; PRA = plasma renin activity; U_{Na^+} = urinary sodium.

*Hyperglycemia produced by intravenous infusion of dextrose in water has been reported to lower plasma AVP while mannitol stimulates AVP secretion.
†AVP is elevated in relation to the concomitant level of plasma osmolality.
‡U_{Na^+} is low in extrarenal salt depletion and elevated in renal salt washing.

Under these conditions, the accumulation of osmoles in the ECF draws water from the cells which results in dilution of the sodium (in the serum or ECF). This type of hyponatremia has been designated cellular dehydration hyponatremia, and the magnitude of the depression of serum sodium can be calculated by multiplying the elevation in plasma glucose greater than 100 mg per dl by 0.016; that is, for every increase of 100 mg per dl in plasma glucose, the sodium will be diluted 1.6 mEq per liter.[248] Under most other conditions, hyponatremia signifies hyposmolality. This does not imply, however, that a single disease process or entity is responsible. The hyposmolar states can be further divided into three subcategories according to the status of the body sodium and water compartments (Table 14). The first category, which probably accounts for less than 30 percent of patients with hyponatremia, has been designated *hypovolemic hyponatremia or hypotonic dehydration.* In this condition there is a significant deficit of total body water, but there is an even larger deficit of total body sodium, the latter occurring by either renal or extrarenal routes. Clinically, the patients show signs of ECF volume depletion coexistent with expansion of intracellular fluid (ICF). Under these circumstances there is a pronounced reduction in ECF volume which, in turn, stimulates the renin-angiotensin system, thirst and the nonosmolar or volume activation of AVP release. This is combined with a reduction in GFR, enhanced tubular reabsorption of salt, and sodium and chloride concentration in the urine of usually less than 10 mEq per liter (unless the sodium loss occurred through the kidneys). The laboratory findings in this disorder are shown in Table 14 and Figure 41. This syndrome can sometimes occur in the absence of AVP, although AVP levels are frequently elevated in hypotonic dehydration. Earlier, we discussed the fact that moderately hypertonic urine and oliguria can be produced in the absence of AVP if the volume of salt and water delivered to the ultimate segments of the nephron is substantially reduced. In fact, in a severely sodium-depleted, congenital (Brattleboro) DI rat allowed free access to water, a degree of hyponatremia and oliguria may develop that is almost indistinguishable from that of a salt-depleted non-DI rat allowed free access to water (Figure 42).[249]

The second category probably accounts for at least 60 percent of patients with hyponatremia in hospitals. It is due, basically, to a primary excess of total body water associated with a nor-

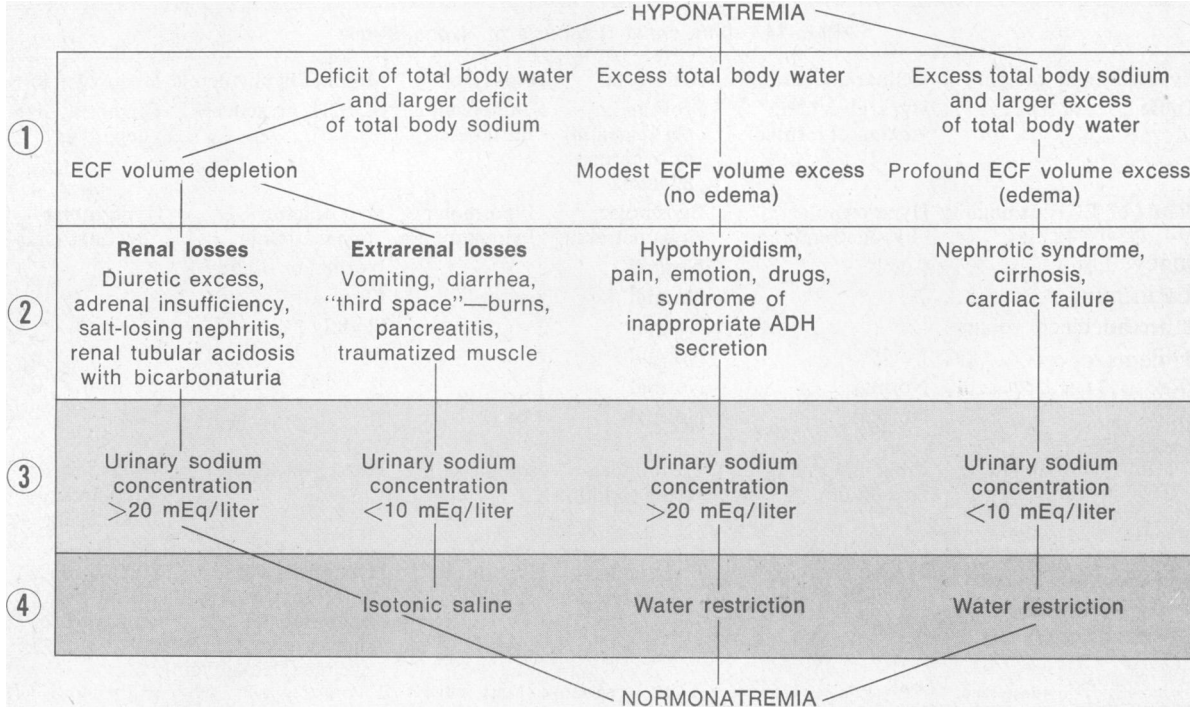


Figure 41.—Diagnostic and therapeutic approach to hyponatremia. ECF = extracellular fluid. (Reprinted with permission from Schrier R, Berl T: Disorders of water metabolism, *In* Schrier RW (Ed): Renal and Electrolyte Disorders, Boston, Little, Brown & Co, 1976, p 36.)

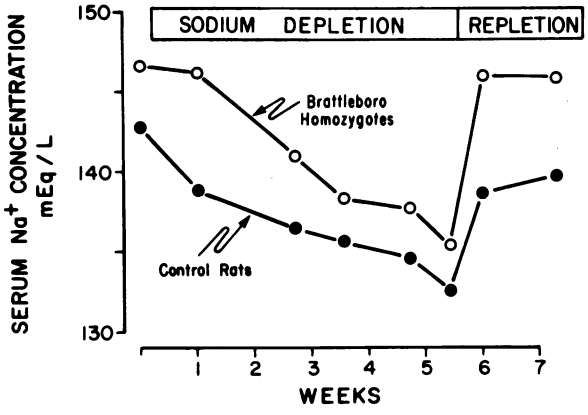


Figure 42.—Development of hyponatremia during NaCl depletion in seven control rats and eight Brattleboro homozygotes. Similarity of responses suggests that vasopressin is not required for selective retention of water seen during sodium depletion. (Data from Harrington AR: Am J Physiol 222:768, 1972. Reproduced with permission from: Valtin J, et al: Recent Progress in Hormone Research 31:466, 1975.)

mal or slightly decreased total body sodium. This condition has been designated *hyponatremia with minimal hypervolemia.* Under these conditions there is an across-the-board expansion of intravascular, interstitial and ICF compartments proportional to their relative sizes; that is, each compartment is increased by the same fractional amount. These patients have a primary defect in the renal excretion of free water. The clinical and laboratory characteristics of these patients are described in Table 14 and Figure 41.

Excluding patients with chronic renal failure, in whom impaired water excretion may result simply from a substantial reduction in renal mass,[250] there remain those patients in whom water excretion is inadequate despite a structurally intact kidney. This failure could be due to (1) an alteration in renal function, which prevents the delivery of an adequate volume of water to the diluting segments of the nephron (ascending limb of the loop of Henle, distal convoluted and collecting tubules) (Table 15); (2) an abnormal permeability of these segments to water despite the absence of circulating ADH (arginine vasopressin), or a substance such as oxytocin which in high concentration can mimic the effect of AVP on the nephron; such an abnormal permeability *may* be present in patients or animals with a deficiency of adrenal glucocorticoids, such as cortisol, or (3) a sustained level of circulating AVP which causes an increased permeability to water of the distal convoluted tubule and collecting duct.

Each of these conditions could make the urine more concentrated and lower in volume than is *appropriate for a given solute and water intake,* thereby resulting in abnormal water retention and hyposmolality of body fluids. While the second condition described above may be confined to adrenal cortical insufficiency,[251] the first and third conditions may frequently be present together and result in a greater impairment in water excretion than in either circumstance alone.[250,252] In fact, at

TABLE 15.—*Physiologic and Pathologic Factors Altering Maximal Water Diuresis and Urinary Dilution Independent of AVP*

Rigid sodium restriction or sodium depletion impairs water diuresis
- Decreased filtered load of sodium and water
- Enhanced proximal tubular reabsorption of sodium and water
- Decreased delivery of sodium and water to distal tubule
- Decreased velocity of flow to loop of Henle
- Decreased medullary blood flow

Glomerular filtration rate
- Decreased GFR may impair maximal water diuresis by above mechanisms; increased GFR does the reverse

Medullary blood flow
- Decreased medullary blood flow impairs maximal water diuresis by increasing hypertonicity of medulla which allows increased back diffusion of water in descending limb and collecting duct in absence of AVP; increased medullary blood does the reverse

Osmotic diuresis
- Increases water diuresis (free water clearance) but causes an increase (less dilute) in minimal urinary osmolality because of increased delivery of solute and water to diluting segments

Diuretics
- Impair maximal urinary dilution and water diuresis:
  - Induce sodium depletion with resultant changes
  - Selectively block sodium resorption by the cortical diluting segment (thiazides) or in the ascending limb (furosemide, ethacrynic acid, ? mercurials) as well

Chronic renal failure
- Impairs maximal diuresis and urinary dilution by:
  - Decrease in number of functioning nephrons
  - Increase in osmotic load per nephron

Primary or secondary adrenal glucocorticoid deficiency
- Impairs maximal water diuresis and urinary dilution:
  - Decrease in GFR and (?) medullary blood flow
  - Enhancement of back diffusion of water in the diluting segments of the nephron in absence of AVP
  - Inappropriate secretion of AVP on basis of volume depletion or ? stress

Hypothyroidism
- Impairs water diuresis by:
  - Decrease in GFR and (?) renal medullary blood flow
  - (?) Inappropriate secretion of AVP

Prostaglandin "deficiency"
- Administration of PGE synthetase inhibitors such as indomethacin

AVP = arginine vasopresssin; GFR = glomerular filtration rate; PGE = prostaglandin E.

times all three situations may contribute to the defect in water excretion almost invariably present in primary or secondary adrenal insufficiency.[250,251] The abnormalities in renal function mentioned could prevent a *necessary* water diuresis, the urine being relatively low in volume and *less* hypotonic than it should be—perhaps, being even moderately hypertonic. Confronted with this situation, one might be unable to determine whether the impaired diuresis is the result of an *inappropriate* circulating level of AVP or some other antidiuretic material, an altered renal function or a combination of both. Bartter and Schwartz, in their original review of hyposmolar syndromes,[252] stressed the importance of a critical evaluation of the nonhormonal factors presented previously and the need for a more specific identification of the antidiuretic activity detected in the biologic fluids of certain of these patients.

Appropriate and Inappropriate Release of AVP

The known regulators of AVP secretion were discussed earlier (see Table 3 in Part I) and, at this point, it is necessary to clarify the meaning of the term *inappropriate*. The final common pathway is made up of the nerve cell bodies of the hypothalamic supraoptic nuclei, and the rate of hormone release at any moment will be the algebraic sum of its stimulatory and inhibitory impulses. We have stressed the continuous delicate balance that exists between osmotic and nonosmotic (such as baroreceptor, chemoreceptor and thermoreceptor) stimuli impinging on this final common pathway. We know that normally a positive water balance, with its consequent drop in the osmolality of blood perfusing the hypothalamic osmoreceptors, will inhibit the release of AVP to a degree necessary to establish normal water diuresis (see Table 7 in Part II). As mentioned earlier, small amounts of AVP may continue to be released into the circulation at this time owing to the tonic stimulation of the nonosmotic baroreceptors (see Table 3 in Part I). However, if a significant fall in blood pressure or cardiac output, a decrease or redistribution of blood volume or a combination of both causes a sustained change in impulses from these receptors, AVP release will be maintained at a higher level despite the positive water balance, and the necessary water diuresis will not occur.

Table 16 distinguishes between *appropriate* release of ADH in response to nonosmotic stimuli and the truly *inappropriate* release of antidiuretic peptides, whether derived from the neurohypophysis or from an ectopic source such as a malignant tumor that is producing AVP. It is important to emphasize that the states listed in Table 16 which also lead to hyponatremia are the same as those in which functional alterations in renal hemodynamics and the renal handling of solutes and water may impair water diuresis *in the absence of any circulating antidiuretic material.*

The sustained release of AVP in these syndromes

TABLE 16.—*Clinical Hyposmolar States Associated With Measured or Probable Increased Secretion of ADH*

States in which ADH may be released (appropriately) in response to the nonosmotic stimuli: Decreased arterial pressure (? pulse pressure) in carotid and, possibly, aortic baroreceptors; decrease in tension in the left atrial wall and great pulmonary veins.

Hypovolemia, hypotension and decreased cardiac output secondary to blood loss or loss of extracellular volume of any cause

Intrinsic myocardial disease of any cause with reduced cardiac output of acute or chronic nature, edematous states with hyponatremia (enhanced proximal tubular resorption of salt and water may at times be more important than increased ADH secretion in the impaired water excretion)

- Cirrhosis with ascites or after large paracentesis*
- Nephrotic syndrome with hypoalbuminemia and hypovolemia
- Congestive heart failure
- Postmural valvulotomy, with (?) relief of distention of left atrial receptors (Table 3)*

States in which ADH secretion may be increased despite the absence of appropriate stimuli (Table 3) ("inappropriate" ADH syndrome): Bronchogenic carcinoma,* adenocarcinoma of the pancreas,* lymphosarcoma, duodenal adenocarcinoma,* pulmonary tuberculosis, pulmonary abscess,* subdural hematoma,* brain tumors,* subarachnoid hemorrhage,* cerebral vascular thrombosis,* skull fractures,* cerebral atrophy,* central pontine myelinolysis,* paroxysmal seizure disorders, acute psychoses,* herpes simplex encephalitis, administration of large quantities of oxytocin and water to obstetric patients, Guillain-Barré syndrome, tuberculosis meningitis, purulent meningitis, acute intermittent porphyria,* myxedema,* postoperative ADH release due to morphine, barbiturates,* cyclophosphamide, vincristine,* carbamazepine,* anesthesia or surgical stress,* transient "idiopathic" hyponatremia (secondary to diuretics, especially thiazides*), and ADH release after surgical procedures* and after hypophysectomy.*

Hyponatremic states with absolute or relative overhydration in which factors other than sustained inappropriate ADH secretion may be responsible for impaired water excretion

Primary and secondary adrenal (glucocorticoid) insufficiency

Chlorpropamide* and, rarely, tolbutamide ingestion

ADH = antidiuretic hormone

*Increased levels of ADH have been measured in serum, urine or tumor extracts by bioassay or immunoassay.

is due to one or more of the following: (1) An abnormal stimulation, by CNS dysfunction or disease, pain, drugs, or psychosis (see Table 3 in Part I), of those areas of the reticular formation, limbic system or cerebral cortex which have neural connections with the hypothalamic, supraoptic and paraventricular nuclei; (2) the stimulation of the nonosmotic mechanisms as listed in Table 3 (see Part I) or (3) tumors of varied causes that have been observed by analysis of the tumor, plasma or urine to contain an antidiuretic material biologically indistinguishable from AVP (Table 16). Those disorders in which AVP is secreted independently of known osmotic or nonosmotic pathways, as described in the first and third conditions above, are called syndromes of inappropriate secretion of ADH (SIADH).

In Table 16, asterisks designate those clinical states in which antidiuretic activity has been detected in plasma, urine or tissue extracts by bioassay,[253] radioimmunoassay, or both.[245,253,254] (Some of these studies have been reviewed by Bartter and Schwartz.[252]) Table 17 presents findings in patients with neoplastic disease and SIADH.[253] In five of the patients, significant quantities of antidiuretic material were extracted from the original tumor or its metastases. This material was identified as arginine vasopressin by immunoassay in four, and by complete inactivation of the antidiuretic activity by human pregnancy plasma (vasopressinase) and rabbit vasopressin antisera in all five. Although the concentration of AVP per milligram of dried powder (47 to 763 units) is only a fraction of that in the human neurohy-

TABLE 17.—*Characteristics of Tissue, Plasma and Tumor Antidiuretic Principle From Patients With Inappropriate ADH Syndrome**

	Antidiuretic Activity μU/mg Powder				*Milk-Ejection Activity μU/mg Powder*	
			After Incubation			*After Incubation*
Specimen	*Bioassay*	*Immunoassay*	*HPP*	*VAR*		*VAR*
• Bronchogenic carcinoma	763±53†	610	ϕ	ϕ	169± 7	ϕ
Normal lung	ϕ				ϕ	
• Bronchogenic carcinoma	162±13	116	ϕ	ϕ	58± 8	ϕ
Hepatic metastasis	ϕ	10			ϕ	
Normal lung	ϕ	<3			ϕ	
Normal liver	ϕ	<4			ϕ	
Plasma	15/ml		ϕ			
• Bronchogenic carcinoma	150±14		ϕ	ϕ		
Liver metastasis	ϕ	<4				
Plasma	ϕ					
• Bronchogenic carcinoma	130±10		ϕ	ϕ	ϕ	
Breast metastasis	740±76	1,540	ϕ	ϕ	124±11	ϕ
Mediastinal metastasis	283±19	120	ϕ	ϕ	48± 2	ϕ
Brain metastasis	307±72		ϕ	ϕ		
Kidney metastasis	ϕ				ϕ	
Normal lung	ϕ				ϕ	
• Adenocarcinoma of pancreas	ϕ				ϕ	
Hepatic metastasis	47± 7	24	ϕ	ϕ	ϕ	
Plasma	8/ml					
• Bronchogenic carcinoma	ϕ	<20			ϕ	
Hepatic metastasis	ϕ	<1			ϕ	
Normal lung	ϕ	<5			ϕ	
Normal liver	ϕ	<3			ϕ	
• Bronchogenic carcinoma						
Biopsy	ϕ				ϕ	
Autopsy	ϕ				ϕ	
Plasma	ϕ				ϕ	
• Bronchogenic carcinoma	ϕ	<4			ϕ	
• Bronchogenic carcinoma	ϕ	<4			ϕ	
Plasma	10/ml		ϕ			
• Bronchogenic carcinoma	ϕ	<5			ϕ	

HPP = human pregnancy plasma, VAR = vasopressin antiserum from rabbit, ϕ = <10-20 μU/mg powder for vasopressin and <12.5-25 μU/mg powder for oxytocin.

*Reprinted with permission from Vorherr et al.[253]
†Mean values±standard error were calculated from values obtained in three to five rats. For each rat the average of several assays was used.

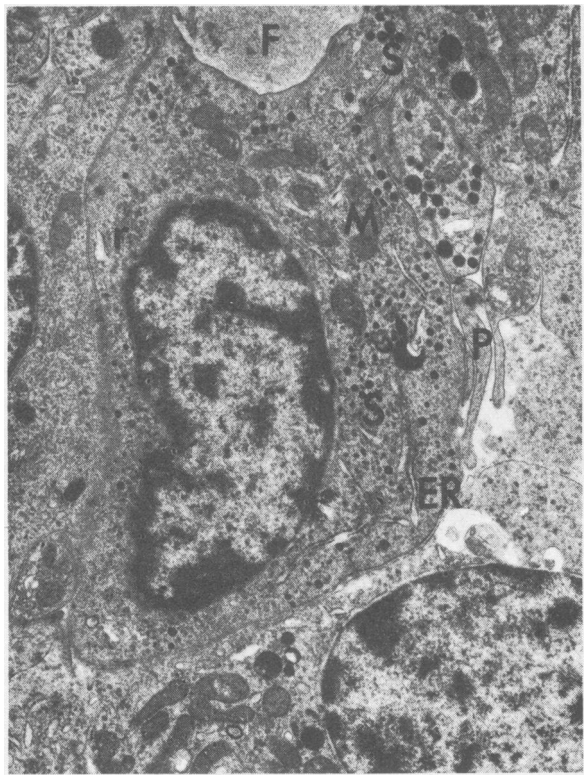


Figure 43.—Neoplastic cell with numerous intracytoplasmic secretory granules (S) and long profiles of endoplasmic reticulum (ER) with attached ribosomes. These cells were observed less frequently than the poorly differentiated neoplastic cells (at left and bottom). In addition to the secretion granules, large mitochondria (M) and aggregations of free ribosomes (r) were present in the cytoplasm. Cytoplasmic projections (P) extended into the prominent intracellular spaces which often contained a network of intermeshed fibrils (F) (reduced from ×11,300). (Reproduced with permission from George JM, et al.[255])

pophysis (85 mU per mg of dried powder), the total mass of the tumor is so great that it is capable of releasing enough hormone to cause a sustained inappropriate AVP syndrome. It should be emphasized that in five patients (Table 17), despite the classic hyposmolar syndrome, no antidiuretic activity was detected in their tumors. Either the syndrome in these cases was due to sustained nonosmotic release of AVP from the neurohypophysis, or the concentration of the hormone in the tumor at the time of extraction was too low to be detected by the assay procedures.

The presence of AVP in tumor extracts, blood and urine, although strongly suggestive that the tumor is the source of the inappropriate AVP *secretion,* is not final proof. The latter requires verification that the tumor is actually capable of producing the hormone. This has been achieved by George and co-workers.[255] They studied an extract of bronchogenic carcinoma that had been removed from a patient with the classic syndrome of inappropriate secretion of AVP and found 23.5 mU of vasopressin per gram of wet weight by radioimmunoassay. Slices of the tumor were incubated with phenylalanine-3H and arginine-vasopressin-3H was purified from the incubate, thus showing in vitro biosynthesis of vasopressin by the tumor. On electron microscopy the small undifferentiated cells of the tumor had well-developed endoplasmic reticulum and ribosomes. Secretion granules surrounded by limiting membranes were present which resembled those seen in polypeptide hormone-secreting cells (Figure 43). Vorherr[256] has recently added additional proof that malignant tumors can be the source of the AVP.

Chronic pulmonary tuberculosis was one of the earliest described causes of the hyposmolar syndrome referred to as "pulmonary salt wasting."[252] Vorherr and associates[257] have clearly shown the presence of vasopressin in tubercular lung tissue from a patient with advanced pulmonary tuberculosis and a typical syndrome of inappropriate secretion of AVP. The extracted tissue contained 22 units of vasopressin per milligram of dried extract. The uninvolved lung tissue, the suspension of *Mycobacterium tuberculosis* and the culture with its metabolites failed to show antidiuretic activity. This is the first case in which a relationship between AVP and hyponatremia in a patient with pulmonary tuberculosis has been shown. Pulmonary diseases of other etiologies have been associated with SIADH. These include chronic obstructive pulmonary disease with emphysema, acute lobar pneumonia and empyema. In some of these syndromes it has been suggested that AVP release might be provoked by impaired pulmonary compliance and some diminished stretch of the great pulmonary vein or left atrial receptors.

Pathophysiology of Water Retention in Minimal Hypervolemic Hyponatremia

The hyposmolar syndromes may or may not be associated with overt edema or reduction in the renal hemodynamics, neither of which is essential to the development of the water retention and hyposmolar state. The mechanism in the nonedematous cases is identical to that which results from the continuous administration of exogenous vasopressin (Pitressin) to normal subjects ingest-

ing a constant and liberal amount of water (Figure 44).[258] The patients are found to have hyponatremia, hypochloremia, normal or low blood urea and creatinine (unless a separate cause for renal impairement exists), mild to moderate oliguria, and a urinary excretion of sodium in excess of 25 mEq per 24 hours, or approximating intake. Note that although the dose of vasopressin was constant throughout the experiment with the normal subjects, urinary osmolality and oliguria were considerably greater in the first few days of its administration (Figure 44). Subsequently, urine volume rose and the concentration of the urine, although still hypertonic, approached the pre-Pitressin period. This *escape* from the maximal renal effect of the hormone must be related to the intrarenal and extrarenal response to the progressive expansion of total body water. It is referred to by Bartter and Schwartz[252] as a new "steady state" in which the degree of hyposmolality or hyponatremia may range from slight to as low as 100 to 110 mEq per liter. During this period urinary sodium usually reflects intake. Although it is evident that the new steady state protects the patient from even more severe degrees of oliguria and water retention, the hyposmolar syndrome will persist as long as a normal water diuresis cannot occur or the patient remains in positive water balance.

Rigid restriction of water (negative water balance) returns the serum sodium level to normal in association with a prompt and substantial reduction in sodium excretion (Figure 44). The cause of the relatively high urinary sodium or the sodium loss has been attributed in part to hypervolemic inhibition of aldosterone secretion in association with an actual increase in the GFR and the filtered load of sodium.[252] However, in some patients urinary aldosterone excretion and GFR have been within normal range despite the continued urinary loss of sodium, indicating that some additional mechanism must be present.[117,118] Fichman and co-workers have reported that although plasma renin activity is considerably suppressed in cases of SIADH or after administration of Pitressin, plasma aldosterone levels are normal and fully responsive to endogenous and exogenous stimuli. It would appear that the most reasonable explanation for the enhanced loss of sodium in SIADH is that the increased total body fluid with expansion of the plasma and extracellular volume causes an inhibition of tubular reabsorption of sodium which may cause enhanced excretion of sodium despite continued secretion of aldosterone.[117,118]

Nolph and Schrier[259] carried out a careful and accurate balance study on a patient with cerebrovascular disease and a syndrome of inappropriate

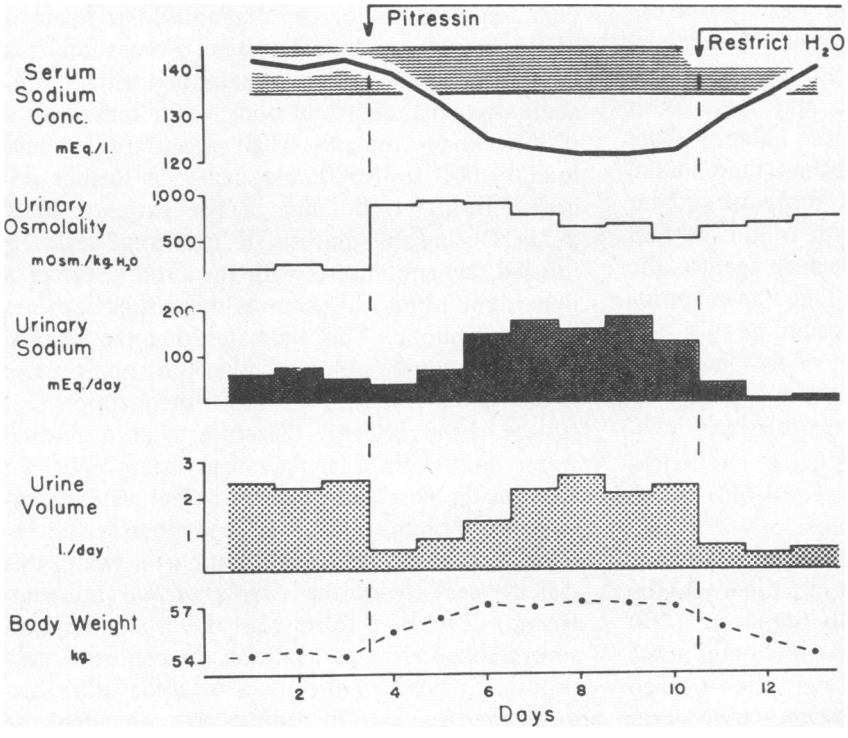


Figure 44.—Diagrammatic summary of the effects of Pitressin and water administration to normal subjects. (Reproduced with permission from Goldberg M: Med Clin N Amer 47:915, 1963.)

secretion of AVP. The results of their study are most helpful in explaining some of the unusual biochemical features of the syndrome. Weight gain and decreased plasma sodium always occurred when the daily fluid intake was 25 ml per kg, causing a gradual expansion of body fluids; 30 ml per kg led to a rapid expansion. The latter caused a sudden increase in sodium excretion, whereas the gradual expansion resulted in minimal, if any, increase in sodium excretion. Aldosterone excretion rates were normal during the control and volume expansion periods. The authors concluded that negative sodium balance, owing to renal loss of sodium, did not contribute substantially to the hyponatremia with either gradual or rapid expansion. During both states, estimated net positive water balance greatly exceeded the actual weight gain. We have observed this phenomenon as well. Because the patient was receiving an isocaloric diet throughout the study, the results suggest that the positive water balance in this syndrome may enhance pulmonary and cutaneous insensible water loss so that more water is retained by balance than is actually calculated from weight gain. During water restriction and recovery from hyponatremia, sodium excretion was well below the control level. This was associated with a rapid return of the plasma sodium concentration to normal over several days with *only slight weight loss relative to the weight gain* that occurred during the previous water expansion period. Aldosterone excretion increased during the recovery period and, together with increased proximal resorption, may have been responsible for the positive sodium balance. During a period of gradual expansion (fluid intake 25 ml per kg), if the patient's intake of sodium was high, isonatremic volume expansion occurred. Positive sodium balance protected against the development of hyponatremia. Thus, an inappropriate retention of water can occur in this syndrome *without* the development of hyponatremia if the rate of fluid ingested is not too great and if the patient's intake of sodium is relatively high.

It should be stressed that for a water intoxication syndrome to develop, there must only be an inability to achieve a water diuresis when hyposmolality of the body fluids exists. Although hypertonic urine is frequently present, a patient may be excreting isotonic or even slightly hypotonic (200 to 250 mOsm per liter) urine. At this point acute expansion of the ECF with *isotonic* saline (which is actually hypertonic to the patient) may paradoxically cause a mild water diuresis, with the urine becoming even more hypotonic. This has been observed when the inappropriate secretion of AVP is due to a bronchogenic carcinoma.[252] If the latter is secreting AVP, it is unlikely that volume expansion would inhibit the release of the hormone from the tumor. Therefore, the paradoxical water diuresis is probably due to a renal "escape" from the antidiuretic effect. As mentioned by Bartter and Schwartz, "an analogous 'escape' is seen in normal dogs given infusions of saline and vasopressin and has been attributed to an increase in tubular flow of a magnitude such that there is inadequate time for osmotic equilibration in the distal portion of the nephron."[252]

At times, however, when a sustained nonosmotic release of AVP from the neurohypophysis is the cause of the hyposmolar syndrome, the patient may respond to the water load with a normal water diuresis. This suggests that the patient is now able to regulate the release of AVP but only in the presence of the expanded total body water and hyponatremia. At this point the subject may respond in a normal fashion to a test load of water. This phenomenon might be anticipated from our earlier discussion of the continuous sensitive interrelationship between osmolar and nonosmolar stimuli controlling the release of AVP. There is a "resetting" of the "osmostat" created by the nonosmotic impulses impinging on the final common pathway or the magnocellular neurons of the neurohypophyseal system. For example, a cirrhotic patient with hyponatremia with a substantially expanded total body water may have a distinct water diuresis when a sustained water load (1,000 to 1,500 ml) causes a further decrease in the osmolality of the patient's body fluids. During this diuresis, if hypertonic saline is infused, an antidiuresis with the production of a hypertonic urine will occur as the serum becomes less hyposmotic. This indicates that the normal osmotic stimuli now produce an appropriate homeostatic response of the neurohypophyseal system. It is evident, therefore, that a normal water diuresis in this new steady state does not rule out the possibility that the initial water retention was produced by sustained nonosmotic release of AVP. An edematous patient in whom this water-excess syndrome *(hypervolemic hypernatremia)* develops (Table 13), in association with severe congestive heart failure, the nephrotic syndrome, cirrhosis of the liver, or some other disorder that functionally reduces GFR, enhances the

release of aldosterone and inhibits the humoral natriuretic "third factor,"[117,118] may have urine that is free of sodium rather than have the "salt-wasting" phase described above.

A most unusual example of the conversion of a salt-wasting to a salt-retaining state was described by Heinermann and Laragh.[260] Two cases of neoplastic disease (oat cell carcinoma of the lung and adenocarcinoma of the stomach) accompanied by the syndrome of hyponatremia, including excessive renal sodium loss, were studied. Both patients had normal renal and adrenal function, which in one was unquestionably due to a sustained inappropriate secretion of AVP. While under observation occlusion of the vena cava developed in both patients, and the hyponatremic salt-wasting state was converted to one of progressive sodium retention and edema formation. In the one with an occlusion of the superior vena cava, the salt retention occurred without an increase in aldosterone secretion; in the other with occlusion of the inferior vena cava, the edema formation occurred in association with hypersecretion of aldosterone. Thus, the disorders of these two patients closely resembled the hyposmolar syndrome seen in other edematous states.

Most recently an increasing number of reports of diuretic-induced (especially thiazide) and chlorpropamide-induced hyponatremic water intoxication syndromes have appeared.[133,229,261-264] Fichman and colleagues[133] studied 25 cases of severe hyponatremia resulting primarily from the use of thiazide diuretics in nonedematous patients without signs of dehydration and with normal creatinine clearance. These cases could be distinguished from other hyponatremic syndromes (Tables 14, 15, 18 and Figure 41) by the presence of hypokalemia and alkalosis, the return of serum sodium to normal and unimpaired excretion of a water load within 3 to 10 days after withdrawing the diuretic, and the recurrence of hyponatremia within 2 to 12 days of readministering the drug (Figure 45). Bioassays of the plasma while the patients were severely hyponatremic showed elevated AVP levels in all ten patients. In Figure 46, the concentration of AVP in these patients is compared with that found in the plasma of 23 cases of the typical syndrome of inappropriate secretion of AVP of varied cause and that of ten patients with secondary adrenal insufficiency associated with pituitary disease. Simultaneous isotope dilution studies in ten of the patients with diuretic-induced hyponatremia showed a substantial decrease in exchangeable potassium, but only a borderline decrease in exchangeable sodium. Increasing potassium intake improved the hyponatremia or prevented its development. The authors concluded that these patients represented a small proportion of those ingesting diuretics in whom potassium depletion rapidly developed after relatively small doses of the drug. The minimal and usual diuretic-induced sodium loss, when associated with hypokalemia and potassium depletion, possibly caused an exaggerated and sustained stimulation of the baroreceptor mechanism controlling the release of AVP. The persistent high level of AVP in the circulation was then primarily responsible for the impaired water excretion and its consequences. Other explanations for the abnormal AVP release include a direct effect of potassium deficiency on the neurohypophyseal system or an indirect effect by PGE enhancement on AVP release.[34-36,186] Finally, an impairment of the ability to excrete free water

TABLE 18.—*Differential Diagnosis of Hyponatremia With Normal Hydration**

	Inappropriate ADH Secretion	*Hypopituitarism*	*Hypothyroidism*	*Diuretic-Induced*	*Chlorpropamide-Induced*	*Polydipsic Vomiting*
Creatinine clearance	Normal	Normal or slightly low	Normal or slightly low	Normal or slightly low	Normal	Normal
Serum K^+ potassium	Normal	Normal	Normal	...	Normal	...
Serum bicarbonate	Normal	Normal	Normal	...	Normal	...
Urine Na^+ sodium	...	...	...	Early,later	...	...
Urine osmolality	...	...	...	Early,later	...	...
Metapyrone response	Normal	...	Normal	Normal	Normal	Normal
Water load response	...	...	Delayed	Normal	Delayed	Normal
Treatment	Water restriction	Hydrocortisone	Thyroid	Discontinue diuretics or potassium intake	Discontinue chlorpropamide	Sodium chloride, water restriction

*From Fichman MP, Vorherr H, Kleeman CR, et al: Ann Intern Med 75:853-863, 1971.

may occur in the absence of circulating AVP as thiazide diuretics prevent the reabsorption of sodium salts in the distal convoluted tubule and, possibly, in the cortical collecting duct.[264]

In the section on diabetes insipidus we discussed in detail the mechanism by which chlorpropamide can cause antidiuresis and thereby impair water excretion. Once this effect of the oral hypoglycemic agent was realized, it was not long before hyponatremia and water intoxication were reported, owing to its use in the treatment of diabetes mellitus.[229,262,263] Garcia and associates,[252] after observing two elderly diabetic patients (aged 71 and 76) with this syndrome, gave chlorpropamide to six additional persons with adult-onset diabetes and studied the response to an oral water load before and after drug administration. All the patients had a substantially impaired water diuresis with chlorpropamide. Twenty-three normal subjects, studied in a similar manner, also had a decrease in their maximal water diuresis, but the decrease was significantly less than that observed in the diabetic patients. It is possible that chlorpropamide is capable of greater inhibition of AVP-stimulated renal PGE synthesis in adult-onset diabetic patients than it is in nondiabetic subjects and, therefore, any residual AVP remaining in the circulation in a water-loaded or water-excess state can cause a greater degree of antidiuresis or impaired water excretion in diabetic persons.

The reason why relatively few patients using chlorpropamide develop hyponatremia and water intoxication is unclear. Theoretically, in all patients and normal subjects receiving chlorpropamide, water retention and hyponatremia should be minimal. The drug should initially cause an inappropriate antidiuresis, leading to a mild positive water balance and hyposmolality. This should inhibit the release of AVP on an osmotic basis, initiate a water diuresis and return water balance *almost* to normal. The data reported by Garcia and associates[252] and others[229,263] strongly suggest that in some patients with diabetes mellitus, particularly the elderly, a sustained nonosmotic stimulus to the release of AVP persists despite the substantial positive water balance. The frequent degenerative changes in the cardiovascular system

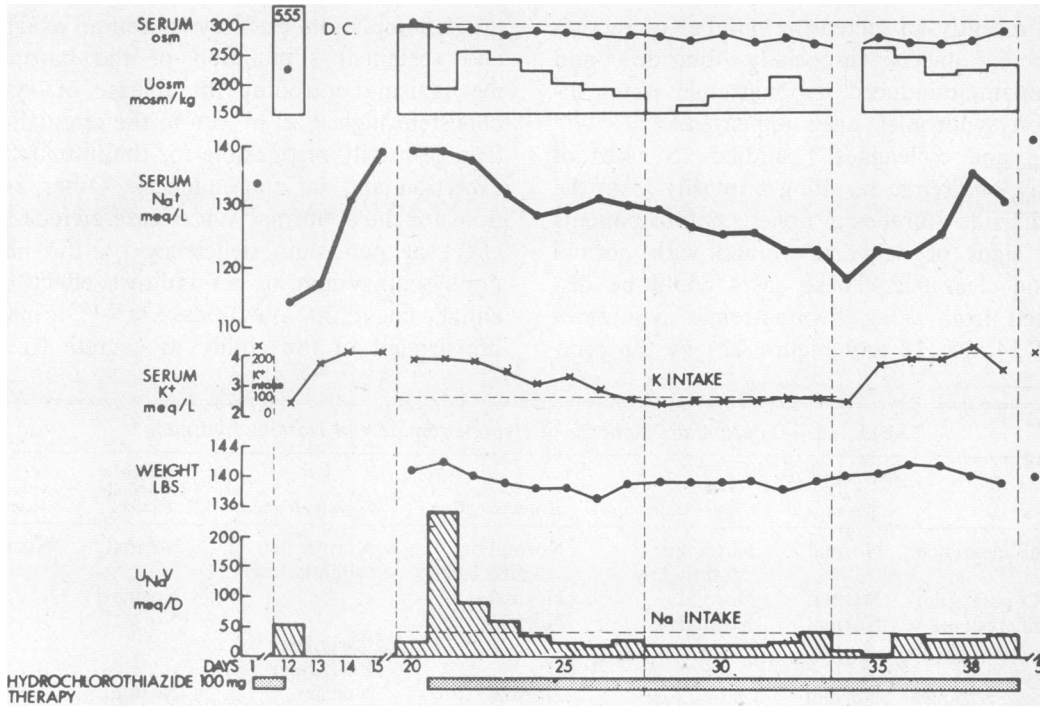


Figure 45.—Improvement in diuretic-induced hyponatremia with potassium (K^+) loading. The crosshatched bars at the bottom of the figure represent the 24-hour urine sodium (Na^+); the horizontal dashed line at the bottom, the Na^+ intake; and the horizontal dashed line in the center, the K^+ intake, which was changed from 80 to 210 mEq per day. At the top of the diagram, the open bars indicate the urinary osmolality; the circles, the serum osmolality, and the dashed line, the normal serum osmolality of 290 mOsm per kg of body weight. (Reproduced with permission from Fichman MP, Vorherr H, Kleeman CR, et al: Ann Intern Med 75:853-863, 1971.)

of diabetic patients may cause abnormal functioning of those baroreceptor mechanisms modulating the secretion of AVP (see Table 3 in Part I). Alternatively, in these patients AVP secretion could be the result of a direct action of chlorpropamide on the CNS.

Studies of two unusual groups of patients with water intoxication have been reported recently. One was a group of patients with beer potomania, all of whom ingested large quantities (many gallons per day) of beer.[265] Coma and other neurologic signs were present, and serum sodium levels ranged between 98 and 120 mEq per liter. The authors concluded that low sodium intake (the "beer diet"), absorption of large quantities of water and, possibly, some form of inappropriate secretion of AVP accounted for the syndrome. It is of interest that several of the patients were also ingesting various types of diuretic drugs for hypertension, possible heart failure or steroid-induced edema. The other group consisted of psychotic patients who appeared to actually "drink themselves" into water intoxication without a known cause for impaired water excretion.[266] It is clear that despite their striking polyuria even those patients with profound polydipsia associated with severe emotional illness in whom a hyposmolar syndrome developed must have had some relative defect in water excretion. If we assume that at normal rates of solute excretion the maximal free water clearance is at least 10 percent of the simultaneous GFR, then a patient with a GFR of 120 ml per minute could excrete 12 ml per minute of free water—that is, clearance of free water would equal 17,280 ml per 24 hours. It is almost inconceivable, therefore, that patients could "drink themselves" into a severe hyposmolar state if there is inhibition of AVP secretion or if the drugs they are therapeutically ingesting can cause a sustained release of AVP that cannot be homeostatically inhibited by hyposmolality of their body fluids. Raskind and co-workers[267,268] have recently reported that plasma AVP levels were elevated in randomly selected untreated psychotic patients (Table 19). However, the mean plasma osmolality of these patients was normal. For dilution of body fluids to occur there must be impairment of water excretion as well as enhanced water intake (in excess of obligatory and insensible losses). The relative infrequency of severe hyponatremia in psychotic patients may be a reflection of normal or reduced water intake. Conversely, enhanced water intake by itself (up to 20 liters per day) is rarely associated with severe hyponatremia.

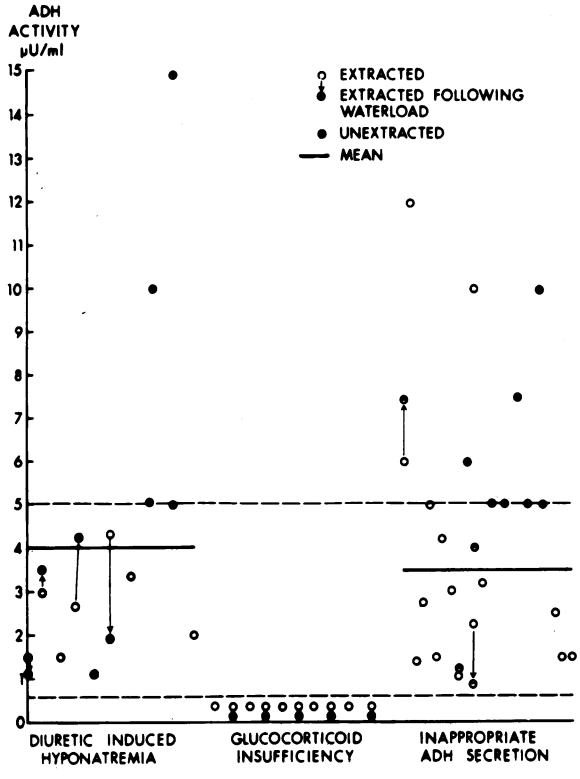


Figure 46.—Results of bioassay for vasopressin activity in plasma samples of 43 patients with hyponatremia caused by diuretics **(left)**, glucocorticoid insufficiency **(middle)** or inappropriate ADH (antidiuretic hormone) secretion **(right)**. The solid circles represent ADH activity in unextracted samples, the open circles ADH activity in extracted samples before water load, and the semisolid circles ADH activity in extracted samples after a water load of 20 ml per kg of body weight, with arrows connecting specimens from the same patient before and after the water load. The dashed lines represent the lower limit of sensitivity of the assay for unextracted (5 μU per ml) and extracted (0.5 μU per ml) samples; the solid horizontal lines represent the mean values for each group. (Reproduced with permission from Fichman MP, Vorherr H, Kleeman CR, et al: Ann Intern Med 75:853-863, 1971.)

In recent years the number of drugs that have been implicated in the production of a state of hyposmolar water retention has increased strikingly. Table 20 lists these drugs and the probable mechanisms by which they impair water excretion. It is certain that the number will increase.

The last major category of hyponatremic states is designated *hypervolemic hyponatremia*. In this situation there is a substantial expansion of total body sodium with even further expansion of total body water. In spite of these elevations, there is a substantial diminution in effective plasma vol-

ume. This is usually the result of decreased cardiac output and high venous pressure as in heart failure and sequestration of ECF volume in the form of ascitic fluid as in cirrhosis. In all these states there is diminished effective renal blood flow which produces substantial sodium retention by both the renin-angiotensin system and renal autoregulatory mechanisms.

The signs and symptoms associated with these conditions will depend, of course, on the underlying disorder that causes the impaired water excretion. The specific manifestations of the hyposmolar state will depend on the rapidity with which it develops and the severity of the hyponatremia. The old and the very young are most susceptible to its adverse effects. If we are dealing with a state of pure water retention that has developed slowly over weeks to months, it is surprising how asymptomatic the patient may be despite concentrations of sodium well below 120 mEq per liter (osmolality usually less than 240 mOsm per liter). However, when hyposmolality of this degree develops rapidly over days to a week or so, the manifestations of disturbed brain function, owing to overhydration of the CNS, may be profound. In addition to progressive depression of the sensorium (confusion, lethargy, headache, stupor and coma), any type of focal neurologic brain syndrome may occur including, finally, focal or generalized convulsions. Recently, Arieff and associates,[269] in a prospective study of a large number of patients with acute (days) and chronic (weeks) hyposmolality, stressed the danger to life of the acute production of water intoxication with concentrations of sodium below 120 mEq per liter. In addition to an in-depth review of this subject, they presented new experimental data on acute and chronic water intoxication in rabbits. The more acutely the same degree of severe hyponatremia (100 mEq per liter) was produced, the higher the mortality. Similar degrees of hyposmolality were very well tolerated by the animals when produced over several days. By analysis of brain tissue for its water, electrolyte and osmole content, Arieff and colleagues showed that when severe hyponatremia developed slowly there was significantly less edema or overhydration of the brain than when it developed rapidly, even when serum sodium levels were the same in the rabbits. The difference was due to the fact that the brain compensated by losing osmoles (sodium, chloride and potassium) when water intoxication was produced more slowly; therefore, less water moved into the brains of these animals on an osmotic differential basis. They "sacrificed" brain solute to prevent brain swelling and death.

TABLE 19.—*Elevated Plasma AVP in Psychosis**

Variable = SEM	*AVP, Units/ml Standing*	*AVP, Units/ml Supine*	*Plasma osmolality, mOsm/kg*	*Number*
Psychotic ..	3.47±0.45†	2.49±0.56	288±2.04	8
Anxious ...	1.6 ±0.23	1.65±0.22	288±1.36	8
Normal control ..	1.71±0.29	1.39±0.31	290±1.60	8

AVP = arginine vasopressin; SEM = standard error of the mean.

*Modified with permission from Raskind M, Weitzman R, Orenstein H, et al: Antidiuretic hormone in psychosis, a pilot study. Biol Psychiatry 13:385-390, 1978.
†P = 0.05

TABLE 20.—*Drugs Associated With Hyponatremia*

Principal Mechanisms

Augmented thirst
- Mellaril (thioridazine)

Augmented renal action of AVP
- Chlorpropamide
- Tolbutamide
- Acetaminophen*
- Phenformin
- Indomethacin*

Impaired renal water excretion independent of AVP
- Chlorpropamide
- Clofibrate
- Carbamazepine
- Vincristine
- Vinblastine
- Cyclophosphamide
- Opiates
- Histamine

Nonosmolar stimulation of AVP release (baroreceptor-mediated)
- Thiazides (?)
- Isoproterenol
- Nicotine
- Barbiturates (?)

AVP = arginine vasopressin

*Enhances AVP action but is not associated with hyponatremia.

Therapy of the Hyponatremic State

Once it is decided into which category a hyponatremic patient belongs, a rational therapeutic approach can be planned. The patient's history preceding the detection of the hyposmolality, symptoms and physical signs, as well as certain critical chemical analyses of blood and urine, when combined with the patient's change in weight and approximated water balance, can permit categorizing the patient's condition (Tables 14, 18 and Figure 41).

Salt- and volume-depleted patients (hypovolemic hyponatremia), when supplied with adequate

amounts of isotonic or, occasionally, hypertonic saline solution, will make whatever final renal adjustments are necessary to maintain ICF and ECF volumes and tonicity at normal levels. This, of course, implies a neurohypophyseal system *appropriately* responsive to the removal of nonosmotic stimuli, and basically normal kidneys that can respond to the neurohumoral adjustments which follow the replacement of salt and water. This is the usual situation associated with an extrarenal cause for the salt and water depletion. Unfortunately, when a functional (excess diuretics, adrenal insufficiency) or organic (salt-losing nephropathy) disorder of the kidney is responsible, the renal adjustment may not be completely appropriate. Therefore, the functional causes must be corrected, and the impact of the organic lesion on the homeostatic excretion of salt and water must be taken into consideration during replacement therapy.

In cases belonging in the second category (hyponatremia with minimal hypervolemia) (Table 14), a primary excess of total body water with normal or minimally decreased total body sodium, once diagnosed, must be corrected by the creation of a negative water balance and, at times, the administration of hypertonic saline to restore the osmolality of body fluids to normal. At the same time that the hyposmolality is being treated, every effort to remove or correct the underlying cause of the impaired water excretion should be made (Tables 15 and 16). Given a patient with a "water excess" syndrome the choice of therapy will depend on the severity of the hyposmolality, the rapidity of its development and the magnitude of the "water intoxication." Basically, a negative water balance must be created, and the first therapeutic maneuver should be the restriction of water intake to the lowest possible level. The drier the diet, the better. In most cases, this will be adequate until the underlying cause can be corrected. Serum sodium and osmolality should be returned to normal levels. Urine volume will decrease further under this therapy, but this will be of no consequence as long as the patient remains in negative water balance through renal and extrarenal routes. The only exception to this approach may be for patients with so-called asymptomatic hyponatremia who have inappropriate or ectopic secretion of AVP and in whom a hyposmolar state has slowly developed over many weeks or longer. In these patients serum sodium levels are between 120 and 130 mEq per liter and CNS and other tissues have adjusted to their hypotonic environment.[269] These patients may not look or feel better when the osmolality of the body fluids is normal. Furthermore, because the underlying cause for the SIADH often cannot be readily removed, hyponatremia will rapidly return when water intake is made more liberal.

In striking contrast to these patients are those who are truly water intoxicated. The impaired water excretion relative to intake, due to the causes listed in Table 16, develops over hours to days and often reaches a point where serum sodium is below 120 mEq per liter. All the symptoms and signs described earlier may present and seriously threaten the life and recovery of these patients. In this situation the foremost objective is to correct the severe cellular overhydration, particularly of the cells of the CNS. This can be accomplished by rapidly (hours) increasing the *effective* osmolality of the ECF while continuing the water-restriction regimen. Hypertonic saline (5 percent) or hypertonic mannitol (10 percent to 20 percent) makes up the effective osmotic solutes. One can estimate the approximate expansion of total body water in these patients by calculating the volume of total body water required to dilute the serum sodium concentration to its observed value. Total body water (BW) is estimated as 60 percent of total weight in women and 65 percent of total weight in men of average body composition. One then multiplies a patient's normal total body weight times a normal total serum sodium concentration and then divides it by the observed serum sodium concentration to get the total body water in the hypotonic state. As mentioned above, such calculations frequently overestimate the true amount of weight gain from the premorbid state.

$$\text{BW} = 70\text{ kg} \times 0.60 = 42\text{ liters}$$
$$X \times 120\text{ mEq/liter} = 42 \times 140\text{ mEq/liter}$$
$$X = 49\text{ liters}$$

Therefore, total BW in the abnormal state (X) is approximately 49 liters, or 7 liters greater than normal. The amount of sodium in milliequivalents required for correction of the hyponatremia can then be calculated by multiplying the difference between the observed sodium concentration and a desired concentration times the total body water. While it is clear that the salt is actually distributed in ECF, the rise in osmolality that it creates at any given point continuously draws water out of the cells along the newly established osmotic gradient until at any given new steady

state the rise in osmolality or sodium concentration is as though the salt were distributed in a volume equivalent to total body water. The serum sodium should be elevated approximately 10 percent to 15 percent over the first eight to ten hours of therapy.

The correction of cellular overhydration will almost always be associated with pronounced improvement in the CNS symptoms and signs during the first 24 hours if they are due to the water intoxication. Occasionally, in older patients (over 65 years), the rate of recovery may be delayed an additional 24 to 48 hours. It is also in this age group that the large salt load and rapid expansion of the extracellular volume, over and above that created by the original water retention may precipitate acute congestive heart failure. This reason and the desire to greatly increase the rate of salt and water excretion, led Hantman and associates[270] to suggest the combined use of hypertonic saline and a potent diuretic such as furosemide (Lasix) at an initial dose of approximately 1 mg per kg of body weight given intravenously. This approach is illustrated in Figure 47. This "loop" diuretic by inhibiting the active reabsorption of sodium chloride in the thick ascending limb (1) prevents excessive ECF volume expansion during and immediately following the saline infusion, (2) substantially impairs the function of the medullary countercurrent multiplier system so that concentrated urine cannot be produced despite the excess circulating AVP and (3) causes the excretion of large amounts of water and sodium in a concentration below that of the plasma and, thus, greatly below that of the administered hypertonic saline. The net effect of this therapy is a large negative water balance produced in a matter of hours associated with a rapid (hours) return of plasma osmolality to normal (Figure 47). An adverse trade-off of this approach is the simultaneous diuretic-induced renal loss of potassium and magnesium ions. This may cause the rapid development of hypokalemia and hypomagnesemia. The former may have immediate deleterious effects which should be anticipated and prevented by simultaneous administration of 150 to 200 mEq per liter of potassium during the first 24 hours of therapy. The excretion of this amount of potassium (in 24 hours) would not be unusual during the diuretic-induced natriuresis. Magnesium excretion may reach 15 to 20 mEq or 180 to 240 mg at the same time. Its rapid development depends on the presence of any degree of hypomagnesium and potassium when serum osmolality and sodium are determined, and the rate of excretion of these ions (magnesium and potassium) during the diuresis.

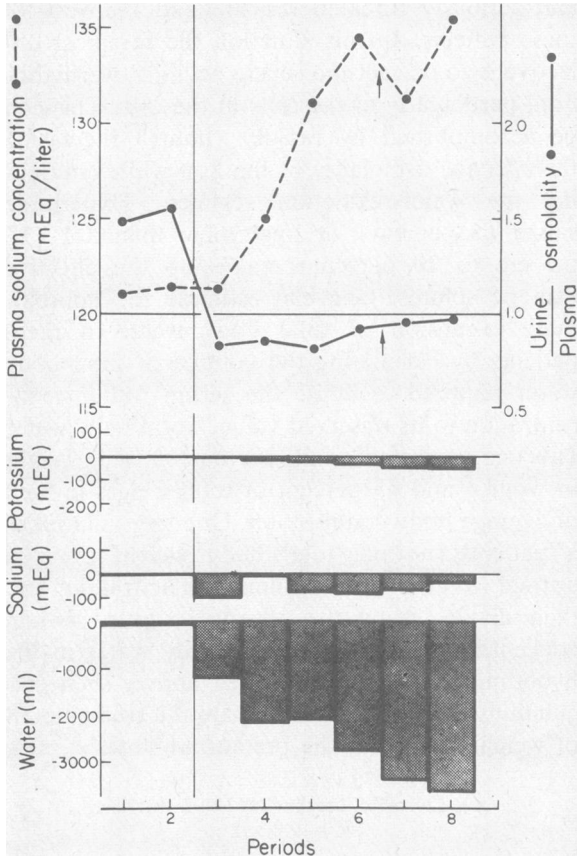


Figure 47.—Use of furosemide and hypertonic saline in the rapid correction of hyponatremia in a patient with the syndrome of inappropriate secretion of antidiuretic hormone. The control periods in this figure are separated from the periods following the administration of furosemide by vertical lines. The arrows indicate the point at which the last dose of furosemide was given. Each period equals one hour. Administration of furosemide was associated with hypotonic urine and increased plasma sodium concentration in the absence of either a positive sodium or positive potassium balance. The cumulative potassium, sodium and water balances are shown in the bottom three panels of the figure. (Reproduced with permission from Hantman D, et al: Ann Intern Med 78:871, 1973.)

Hypertonic mannitol has been suggested as an alternative to hypertonic sodium chloride for the treatment of hyposmolar states, but its use offers no particular advantages and has several possible disadvantages compared with hypertonic saline.[247,271]

Three drugs that specifically inhibit the secretion or renal effect of AVP have been used in the treatment of SIADH. These are diphenylhydantoin

(Dilantin) which when administered intravenously can block the release of AVP from the neurohypophysis,[272] dichlormethyltetracycline (Declomycin, demeclocycline)[273] and lithium.[274] Both of these latter compounds act by directly blocking the renal tubular effect of AVP. They appear to have a role in patients in whom the syndrome is not self-limited and in whom the underlying cause cannot be removed. In such settings (for example, AVP-secreting bronchogenic carcinoma), a drug that could be taken by mouth and for a prolonged period would be most desirable. While both have untoward and toxic effects, the antibiotic dichlormethyltetracycline in dosages of 1 to 2 grams per day would be least objectionable. With greater experience in the use of this drug, we will be better able to define its practical limitations.

Glucocorticoids and Water Excretion

The inability to excrete a water load in a normal manner is characteristic of primary and secondary adrenal insufficiency. This defect is due to a deficiency of cortisol, and it continues to be seen in the presence of a normal extracellular volume and adequate mineralocorticoids.[251] These persons are unable to form a maximally dilute urine or to attain a maximal rate of water diuresis after either an acute or chronic water load and, therefore, are particularly prone to the development of water intoxication. The continued production of a hypertonic urine relatively low in volume during a sustained positive water load suggests the possible presence of continued circulating AVP. However, to date the evidence is still inconclusive in both humans and animals as to the exact role of AVP in the impaired water excretion of primary and secondary adrenal insufficiency. It is clear that if a patient with primary or secondary adrenal insufficiency has hypovolemia, hypotension or reduced cardiac output (see Table 3 in Part I), it could cause a sustained release of AVP which would contribute to an impaired water excretion resulting from a nonhormonal mechanism. Share and Travis[275] showed in trained unanesthetized dogs with excised adrenal glands that if blood and extracellular volume were maintained at normal levels by a liberal intake of sodium chloride, basal plasma AVP concentration did not increase. However, the concentration of AVP in the plasma rose progressively if the sodium chloride was withdrawn. Giving the animal a large dose of hydrocortisone at this point only slightly reduced the elevated AVP levels, whereas an infusion of saline without the steroid administration returned the plasma AVP almost to normal. Additional experimental evidence against a *primary* role of AVP in the impaired water diuresis of adrenal-insufficient humans or animals was given by Green and co-workers[276] who showed that the diuresis is equally impaired in adrenalectomized rats with hereditary DI (Brattleboro strain). Arginine vasopressin *cannot* participate in the defect in water excretion in these adrenal-insufficient animals. Using a sensitive bioassay, our findings indicated a normal disappearance of AVP from the circulation of untreated patients with adrenal insufficiency despite impaired diuresis.[133,251] In these patients there was no delay in activation of, or increased sensitivity to, exogenously administered AVP. Although their peak water diuresis was subnormal, the rate at which this level was attained was comparable to that observed in normal persons.[251] Ahmed and associates[277] and, recently, others[278] have implicated sustained circulating AVP in the impaired water diuresis of primary or secondary adrenal insufficiency. However, it is reasonable to conclude that the sustained circulating AVP is not essential for this defect in water excretion.

If the latter is correct, why do these patients have this physiologic abnormality? Certainly, any reduction in GFR or renal blood flow would impair the attainment of a maximal water diuresis. Both GFR and renal blood flow have been found to be moderately reduced in patients with adrenal insufficiency, and hemodynamic abnormalities are corrected by adequate therapy with glucocorticoids. However, rapid administration of hydrocortisone during impaired water diuresis can substantially improve the rate of urinary flow and the production of a maximally dilute urine with little or no acute alteration in renal hemodynamics.[279] Nonhormonal techniques that considerably improve renal blood flow and GFR, such as aminophylline administration, do not appreciably enhance the water diuresis.[279] These observations suggest that the glucocorticoids improve water diuresis through some intrarenal mechanism that ultimately causes a decrease in the back diffusion of water in the diluting segments of the nephrons. It is also possible that these steroids allow these segments to become maximally impermeable to water in the absence of AVP. This could be considered a "permissive" role of the glucocorticoids.

The pure water-excess syndrome secondary to the sustained release of AVP can be almost mi-

micked by primary and secondary adrenal insufficiency (glucocorticoid deficiency). In the latter circumstances the hyponatremia and relative or absolute excess of total body water can be quickly corrected by the oral or intravenous administration of glucocorticoids; in contrast, the syndrome of inappropriate secretion of AVP not associated with glucocorticoid deficiency will not be corrected by steroid administration.[133,280,281]

REFERENCES

1-142, see Part I, Nov 1979 issue; 142-236, see Part II, Dec 1979 issue

237. Arieff AE, Carroll HJ: Nonketotic hyperosmolar coma with hyperglycemia: Clinical features, pathophysiology, renal function, acid-base balance, plasma-cerebrospinal fluid equilibria and the effects of therapy in 37 cases. Medicine 51:73-94, 1972

238. Boyer J, Gill GN, Epstein FH: Hyperglycemia and hyperosmolality complicating peritoneal dialysis. Ann Intern Med 67: 568-572, 1967

239. DeRubertis FR, Michelis MF, Davis BB: "Essential" hypernatremia—Report of three cases and review of the literature. Arch Intern Med 134:889-895, 1974

240. Trust PM, Brown JJ, Chinn RH, et al: A case of hypopituitarism with diabetes insipidus and loss of thirst—Role of antidiuretic hormone and angiotensin II in the control of urine flow and osmolality. J Clin Endocrinol Metab 41:346-353. 1975

241. Schalekamp M, Donker S, Jansen-Goemans A, et al: Dissociation of renin and aldosterone during dehydration: Studies in a case of diabetes insipidus and adipsia. J Clin Endocrinol Metab 43:287-294, 1976

242. Sridhar CB, Calvert GD, Ibbertson HK: Syndrome of hypernatremia, hypodipsia and partial diabetes insipidus: A new interpretation. J Clin Endocrinol Metab 38:890-901, 1974

243. Grubb SR, Watlington CO, Blackard WG: Osmoreceptor dysfunction, chronic hypernatremia, adipsia and vasopressin resistant diabetes insipidus. Clin Res 25:13a, 1977

244. Halter J, Goldberg A, Robertson G, et al: Selective osmoreceptor dysfunction in the syndrome of chronic hypernatremia and hypodipsia. Endocrinology 98 (Suppl):159, 1976

245. Macaulay D, Watson M: Hypernatremia in infants as a cause of brain damage. Arch Dis Child 42:485-491, 1967

246. Arieff AI, Guisada R, Lazarowitz VC: Pathophysiology of hyperosmolar states, *In* Andreoli TE, Grantham JJ, Rector FC Jr (Eds): Disturbances in Body Fluid Osmolality. Bethesda MD, American Physiology Society, 1977, chapter 11, pp 227-250

247. Covey CM, Arieff AI: Disorders of sodium and water metabolism and their effects on the central nervous system, *In* Brenner BM, Stein JH (Eds): Sodium and Water Homeostasis. New York, Churchill Livingstone, 1978, chapter 9, pp 212-241

248. Katz MA: Hyperglycemia-induced hyponatremia—Calculation of expected serum sodium depression. N Engl J Med 289: 843-844, Oct 18, 1973

249. Valtin H: Genetic models for hypothalamic and nephrogenic diabetes insipidus, *In* Andreoli TE, Grantham JJ, Rector FC Jr (Eds): Disturbances in Body Fluid Osmolality. Bethesda MD, American Physiology Society, 1977, pp 197-215

250. Kleeman CR, Adams DA, Maxwell MH: An evaluation of maximal water diuresis in chronic renal disease—I. On normal solute intake. J Lab Clin Med 58:169-184, 1961

251. Kleeman CR, Czaczkes JW, Cutler R: Mechanisms of impaired water excretion in adrenal and pituitary insufficiency—IV. Antidiuretic hormone in primary and secondary adrenal insufficiency. J Clin Invest 43:1641-1648, 1964

252. Bartter F, Schwartz WB: The syndrome of inappropriate secretion of antidiuretic hormone. Am J Med 42:790-806, 1967

253. Vorherr H, Massry SG, Utiger RD, et al: Antidiuretic principle in malignant tumor extracts from patients with inappropriate ADH syndrome. J Clin Endocrinol 28:162-168, 1968

254. Utiger RD: Inappropriate antidiuresis and carcinoma of the lung—Detection of arginine-vasopressin in tumor extracts by radioimmunoassay. J Clin Endocrinol Metab 26:970-974, 1966

255. George JM, Capen CC, Phillips AS: Biosynthesis of vasopressin in vitro and ultrastructure of a bronchogenic carcinoma. J Clin Invest 51:141-148, 1972

256. Vorherr H: Paraendocrine tumor activity with emphasis on ectopic production of ADH secretion. Oncology 29:382-416, 1974

257. Vorherr H, Massry SG, Fallet R, et al: Antidiuretic principle in tuberculous lung tissue of a patient with pulmonary tuberculosis and hyponatremia. Ann Intern Med 72:383-387, 1970

258. Leaf A, Bartter FC, Santos RF, et al: Evidence in man that urinary electrolyte loss induced by Pitressin is a function of water retention. J Clin Invest 32:868-878, 1953

259. Nolph KD, Schrier RW: Sodium, potassium and water metabolism in the syndrome of inappropriate antidiuretic hormone secretion. Am J Med 49:534-545, 1970

260. Heinermann HO, Laragh JH: Inappropriate renal sodium loss reverted by vena cava obstruction. Ann Intern Med 65:708-718, 1966

261. Beresford HR: Polydipsia, hydrochlorothiazide and water intoxication. JAMA 214:879-883, 1970

262. Garcia M, Miller M, Moses AM: Chlorpropamide-induced water retention in patients with diabetes mellitus. Ann Intern Med 75:549-554, 1971

263. Hagen GA, Frawley TF: Hyponatremia due to sulfonylurea compounds. J Clin Endocrinol 31:570-576, 1970

264. Kennedy RM, Earley LE: Profound hyponatremia resulting from a thiazide-induced decrease in urinary diluting capacity in a patient with primary polydipsia. N Engl J Med 282:1185-1186, 1970

265. Demanet JC, Bonnyns M, Bleiberg H, et al: Coma due to water intoxication in beer drinkers. Lancet 2:1115-1117, 1971

266. Hobson JA, English JT: Case study of a chronically schizophrenic patient with physiological evidence of water retention due to inappropriate release of antidiuretic hormone. Ann Intern Med 58:324-332, 1963

267. Raskind MA, Orenstein H, Christopher G: Acute psychosis, increased water ingestion and inappropriate antidiuretic hormone secretion. Am J Psychol 132:407-410, 1975

268. Raskind MA, Weitzman RE, Fisher DA, et al: Antidiuretic hormone is elevated in psychosis. Biol Psychiatry 13:385-390, 1978

269. Arieff AI, Llach F, Massry SG: Neurological manifestations and morbidity of hyponatremia: Correlation with brain water and electrolytes. Medicine 55:121-129, 1976

270. Hantman D, Rossier B, Zohlman R, et al: Rapid correction of hyponatremia in the syndrome of inappropriate secretion of antidiuretic hormone. Ann Intern Med 78:870-875, 1973

271. Maclean D, Champion M, Trash DB: Pulmonary edema during treatment of acute water intoxication. Postgrad Med J 52: 532-535, 1976

272. Fichman MP, Kleeman CR, Bethune JE: Inhibition of antidiuretic hormone secreted by diphenylhydantoin. Arch Neurol 22:45, 1970

273. Cerrill DA, State RM, Birge JR, et al: Demeclocycline treatment in the syndrome of inappropriate antidiuretic hormone secretion. Ann Intern Med 83:654-656, 1975

274. White ME, Fetner CD: Treatment of the syndrome of inappropriate secretion of antidiuretic hormone with lithium carbonate. N Engl J Med 292:390-392, 1975

275. Share L, Travis RH: Interrelations between the adrenal cortex and the posterior pituitary. Fed Proc 30:1378-1382, 1971

276. Green HH, Harrington AR, Valtin H: On the role of antidiuretic hormone in the inhibition of acute water diuresis in adrenal insufficiency and the effects of gluco- and mineralocorticoids in reversing the inhibition. J Clin Invest 49:1724-1736, 1970

277. Ahmed ABJ, George BC, Gonzalez-Auvert C, et al: Increased plasma arginine vasopressin in clinical adrenocortical insufficiency and its inhibition by glucosteroids. J Clin Invest 46: 111-123, 1967

278. Seif M, Robinson AG, Zimmerman EA, et al: Plasma neurophysin and vasopressin in the rat: Response to adrenalectomy and steroid replacement. Endocrinology 103:1009-1015, 1978

279. Boykin J, McCool A, McDonald K, et al: Mechanism of effect of glucocorticoid deficiency on renal water excretion in the conscious dog (abstract). Clin Res 24:269A, 1976

280. Kleeman CR, Maxwell MH, Rockney RE: Mechanism of impaired water excretion in adrenal and pituitary insufficiency—1. The role of altered glomerular filtration rate and solute excretion. J Clin Invest 37:1799-1812, 1958

281. Fichman MP, Bethune JE: The role of adrenocorticoids in the inappropriate antidiuretic hormone syndrome. Ann Intern Med 86:806-820, 1968